



(19)

Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 0 721 956 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
02.08.2000 Bulletin 2000/31

(51) Int. Cl. 7: C07J 17/00, A61K 31/70,
C07J 43/00, C07J 41/00

(21) Application number: 94927793.3

(86) International application number:
PCT/JP94/01602

(22) Date of filing: 28.09.1994

(87) International publication number:
WO 95/09177 (06.04.1995 Gazette 1995/15)

(54) 21-SUBSTITUTED STEROID COMPOUND

IN STELLUNG 21 SUBSTITUIERTE STEROIDE
COMPOSE STEROIDE SUBSTITUE EN POSITION 21

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL
PT SE

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(30) Priority: 29.09.1993 JP 24312393

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(43) Date of publication of application:
17.07.1996 Bulletin 1996/29

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Description**Field of the Invention**

5 [0001] This invention relates to novel steroid compounds substituted at position-21 with simple sugars or acylated derivatives of said simple sugars.

Background of the Invention

10 [0002] Development of sugar-steroid compounds which have no steroid activities themselves, but can be converted to the active forms by glucosidases which increase at the inflammatory site of rheumatism or the like have been reported by the research group of Merck & Co. [J. Am. Chem. Soc. (1964), 86, 3903-4, FR3627 (1965) and GB1015396 (1965)]. Specifically, GB-A-1015396 relates to 21-glucuronide derivatives of steroids of the pregnane series and discloses in Experiment No. 10 on page 7 the intermediate butyl [(9 α -fluoro-6,16 α -dimethyl-11 β , 17 α -dihydroxy-1,4,6-pregnatriene-3,20-dione-21-yl tri-0-benzoyl- β -D-glucopyranosid] uronate.

15 [0003] Several steroid derivatives aimed to reduce toxicity were also synthesized. For example, a sugar-steroid compound capable of specifically reaching the colon was reported (Japanese Patent Laid-open Publication, Sh60-501105 (WO8404041), J. Pharm. Pharmacol. (1991), 43, 353-5, WO9415947 (published on July 21, 1994) and WO9322334 (published on November 11, 1993). Specifically, WO-A-94/15947, which is comprised in the state of the 20 art in the sense of Article 54(3) EPC discloses in Examples 1-4 certain glycosides of steroid compounds belonging to the pregnane series.

25 [0004] US-A-3,427,300 discloses (in Examples 5 and 6) 21-sugar derivatives of anti-inflammatory steroids which have the hydroxy groups of the 21-sugar group derivatized with O-acetoxy-benzoyl groups, i.e. the hydroxyl groups of the sugar chains are protected with derivatives of acetyl salicylic acid.

30 [0005] Inventors of the present invention actually synthesized glycosyl steroid derivatives wherein simple sugars or said simple sugars with having hydroxyl groups thereof modified with acetyl groups were linked to steroids, and examined their pharmacological activities, confirming that side-effects of these derivatives were about the same as those of the aglycon steroids, and actually not sufficiently reduced probably because they might be readily hydrolyzed by glucosidases usually omnipresent within living body to release the aglycon steroids.

Disclosure of the Invention

35 [0006] The present invention was made in view of the aforementioned problems, aiming to provide sugar-steroid compounds with significantly reduced unfavorable side-effects.

[0007] In order to resolve the above-mentioned problems, the present invention features in the modification of hydroxyl groups of simple sugar component of sugar-steroid compounds with sterically bulky protective groups, more specifically, toluoyl (ortho-, meta-, or para-methylbenzoyl), benzoyl, p-chlorobenzoyl or arylalkyl (e.g., benzyl) groups.

[0008] By the introduction of these bulky protective groups, the resulting sugar-steroid compounds are rendered more resistant to endogenous glycosidases omnipresent in living body, releasing the active aglycon (steroid) only after the cleavage action of glycosidases which are known to increase at the inflammatory site. Therefore, glycosylsteroid derivatives of the present invention are able to exert anti-inflammatory effect without showing unfavorable side-effects on the non-inflammatory sites. Furthermore, this effect is also achieved by limiting simple sugars to be used to those not present or almost not present in living body (e.g., fucose and rhamnose).

[0009] Accordingly, the present invention provides glycosides of steroid compounds as the aglycon, wherein the 45 21-position of said steroid compounds is substituted with simple sugars or acylated derivatives of said simple sugars, the hydroxyl groups of said simple sugars or said acylated simple sugars are protected with toluoyl, benzoyl, p-chlorobenzoyl, or aryl-alkyl groups, and said steroid compounds consist of dexamethasone, beta-methasone, the dideacyl derivative of difluprednate, diflurasone, diflucortolone or betamethasone valerate.

[0010] The present invention also relates to compounds as defined above, for use as an anti-inflammatory agent.

[0011] Further, the present invention relates to glycosides of anti-inflammatory steroid compounds as the aglycon for use as an anti-inflammatory agent, wherein the 21-position of said steroid compounds is substituted with simple sugars or acylated derivatives of said simple sugars, and the hydroxyl groups of said simple sugars or said acylated simple sugars are protected with toluoyl, benzoyl, p-chlorobenzoyl, or aryl-alkyl groups.

[0012] According to one embodiment, glycosylsteroid derivatives of the present invention are glycosides of dexamethasone as the aglycon, wherein position-21 thereof is substituted with simple sugars or acylated sugars selected from a group comprising glucose, galactose, mannose, fucose, rhamnose, N-acetylglucosamine, N-acetylgalactosamine, galacturonic acid, glucuronic acid and sialic acid.

[0013] According to another embodiment, glycosylsteroid derivatives of the present invention are glycosides of bet-

amethasone as the aglycone which are substituted at position-21 thereof with simple sugars or acylated simple sugars selected from a group comprising glucose, galactose, mannose, fucose, N-acetylglucosamine, N-acetylgalactosamine, galacturonic acid, glucuronic acid and sialic acid.

[0014] Moreover, it is preferred that hydroxyl groups of simple sugars or acylated simple sugars in said glycosides, that is, steroid derivatives of the present invention are protected with toluoyl group.

[0015] In addition, of steroid derivatives related to the present invention, the compounds with the following constitutional formulas are especially useful.



[0016] All anti-inflammatory agents comprising said compounds (glycosides) can be used singly or in combination thereof as dermatological ointment, cream, lotion or tape (liniment for external use only). For the treatment of bronchial asthma and allergic rhinitis, they can be used as the intra-oral and intra-nasal inhalation agents, respectively.

[0017] Steroid derivatives (glycosides) of the present invention mentioned above not only have the activities for suppressing the granuloma growth and croton oil-induced ear edema, but also less unfavorable side-effects on weights of body, thymus, spleen or adrenal and on leucocyte counts at the administration or painting of them. Therefore, these agents are less toxic and more highly safe as compared with conventional steroid drugs.

[0018] Steroid derivatives of the present invention can be applied for the treatment of eczema, dermatitis (including keratoderma tylodes palmaris progressiva, female facial melanoderma, lichen Vidal, radiodermatitis and dermatitis solaris), pruritus cutaneus, prurigo (including lichen urticatus, strophulus and urticaria perstans), bug bites, psoriasis, palmoplantar pustulosis, lichen planus, lichen nitidus, pityriasis rubra pilaris, pityriasis rosea Gilbert, erythema group (including erythroderma derived from malignant lymphoma), chronic discoid lupus erythematosus, drug rash/toxicoderma, alopecia areata, burn injury (including cicatrix and keloid), frostbite, dermatitis herpetiformis (Duhring) (including psuedosmallpox (permphigoid)), hemorrhoids, and surgical wounds due to tympanoplasty, fenestration operation and tympanomeatoplasty.

[0019] The aforementioned protected compounds (glycosides) may be prepared by first protecting the starting material simple sugars or acylated simple sugars with toluoyl or acetyl group, replacing position-1 thereof with a halogen atom, and then reacting the sugar halide with dexamethasone or betamethasone in the presence of molecular sieve and Lewis acids such as silver carbonate, silver triflate or tin (VI) chloride. Said compounds (glycosides) may be obtained by deprotecting these protected glycosides with MeONa/MeOH of the like.

[0020] In this case, the use of toluoyl group as the protecting group is advantageous, because said group not only provides the requested product in a better yield by preventing the formation of undesirable ortho ester, but also the toluoyl-protected derivatives themselves have lower undesirable side-effects and higher pharmacological safety.

Brief description of drawings

45 [0021]

Fig. 1 is a flow-chart showing the synthesis route of glucosyldexamethasone.

Fig. 2 is a flow-chart showing the synthesis route of glucosyldexamethasone (ortho ester derivative).

Fig. 3 is a flow-chart showing the synthesis route of galactosyldexamethasone.

50 Fig. 4 is a flow-chart showing the synthesis route of mannosyldexamethasone.

Fig. 5 is a flow-chart showing the synthesis route of β -N-acetylglucosaminyldexamethasone.

Fig. 6 is a flow-chart showing the synthesis route of N-acetylgalactosaminyldexamethasone.

Fig. 7 is a flow-chart showing the synthesis route of β -glucuronyldexamethasone and Tol-protected derivative of β -glucuronyldexamethasone.

55 Fig. 8 is a flow-chart showing the synthesis route of β -galacturonyldexamethasone and Tol-protected derivative of β -galacturonyldexamethasone.

Fig. 9 is a flow-chart showing the synthesis route of β -fucosyldexamethasone.

Fig. 10 is a flow-chart showing the synthesis route of sodium salt of sialyldexamethasone.

Fig. 11 is a flow-chart showing the synthesis route of sialylbetamethasone.
 Fig. 12 is a flow-chart showing the synthesis route of per-Tol-protected derivative of glucosylbetamethasone.
 Fig. 13 is a flow-chart showing the synthesis route of glucosylbetamethasone (*p*-toluoyl derivative).
 Fig. 14 is a flow-chart showing the synthesis route of glucosylbetamethasone (*o*-toluoyl derivative).
 Fig. 15 is a flow-chart showing the synthesis route of glucosylbetamethasone (*m*-toluoyl derivative).
 Fig. 16 is a flow-chart showing the synthesis route of glucosylbetamethasone (benzoyl derivative).
 Fig. 17 is a flow-chart showing the synthesis route of glucosylbetamethasone (benzyl derivative).
 Fig. 18 is a flow-chart showing the synthesis route of glucosyldiflupredonate (*p*-toluoyl derivative).
 Fig. 19 is a flow-chart showing the synthesis route of glucosyldiflorasone (*p*-toluoyl derivative).
 Fig. 20 is a flow-chart showing the synthesis route of glucosyldiflucortolone (*p*-toluoyl derivative).
 Fig. 21 is a flow-chart showing the synthesis route of glucosyldiflucortolone (benzoyl derivative).
 Fig. 22 is a flow-chart showing the synthesis route of glucosyldiflucortolone (*p*-chlorobenzoyl derivative).
 Fig. 23 is a flow-chart showing the synthesis route of glucosyldiflucortolone (acetyl derivative).
 Fig. 24 is a flow-chart showing the synthesis route of glucosyldexamethasone (acetyl derivative).
 Fig. 25 is a flow-chart showing the synthesis route of galactosyldexamethasone (acetyl derivative).
 Fig. 26 is a flow-chart showing the synthesis route of glucosylbetamethasone valerate (*m*-toluoyl derivative).
 Fig. 27 is a flow-chart showing the synthesis route of β -rhamnosyldexamethasone.

Most preferred embodiment for practicing the present invention

[0022] The most preferred embodiments of the present invention will be described below.

1) Synthesis of compounds

[0023] Syntheses of derivatives of dexamethasone and betamethasone are described below. Unless otherwise noted, chemicals used of the reagent grade were purchased from Tokyo Kasei Kogyo Co., LTD.

Example 1

30 Synthesis of glucosyldexamethasone (Fig. 1)

1) Toluoylation of glucose

[0024] D-(+)-glucose 1 (2 g) was dissolved in chloroform (40 ml), and to this solution were added *p*-toluoyl chloride (14.5 ml) and pyridine (8.9 ml) drop-wise at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 6 h. The reaction solution was poured into ice-water and extracted with chloroform. The organic layer was washed successively with saturated solutions of copper sulfate, sodium bicarbonate, and sodium chloride. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. A portion (5.33 g) of the residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 50:1) to give 2 (4.5 g) as white powder.

Compound 2

[0025]

$C_{46}H_{42}O_{11}$ MW = 770.831
 1H -NMR [500 MHz, CDCl₃, Ref = 0.000ppm(TMS)]

(CH₃C₆H₄CO-) x 5 : 8.062, 7.910, 7.834, 7.780, 7.775
 (each 2H, d, J = 8.06)
 7.341, 7.207, 7.156, 7.106, 7.101
 (each 2H, d, J = 8.06)
 (CH₃C₆H₄CO-) x 5 : 2.474, 2.408, 2.362, 2.315, 2.309
 (each 3H, s)

2) Bromination of glucose

[0026] 2 (4.5 g) was dissolved in chloroform (20 ml), and to this solution was added hydrobromic acid-acetic acid

solution (8.8 ml) at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred at room temperature overnight. After the unreacted bromine was removed with an argon stream, the solvent was distilled off *in vacuo*. The residue was dissolved in chloroform, and washed with cold saturated sodium bicarbonate solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo* to yield 3 as pale yellow powder [2.5 g (yield 59.2%)].

Compound 3

[0027]

10

$C_{38}H_{35}O_9Br$ MW = 715.593
 1H -NMR [500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

15	$(CH_3C_6H_4CO) \times 4 :$	7.944, 7.881, 7.830, 7.761 (each 2H, d, $J = 8.06$) 7.236, 7.191, 7.160, 7.094 (each 2H, d, $J = 8.06$)
20	$(CH_3C_6H_4CO) \times 4 :$	2.414, 2.365, 2.357, 2.299 (each 3H, s)
	Position-1 of glucose :	6.849 (1H, d, $J_{1,2} = 4.03$)

3) Synthesis of glucosyldexamethasone

[0028] Dexamethasone (6) (300 mg) was dissolved in tetrahydrofuran (20 ml), and to this solution were added molecular sieve 5A (400 mg) and silver triflate (390 mg). Then, to this mixture was added, under an argon atmosphere and at 0 - 5°C, a glucose bromide (3) (1.10 g) dissolved in tetrahydrofuran (10 ml). While the reaction temperature was slowly raised to room temperature, the resulting mixture was stirred for 2 h. After the reaction solution was filtered, the solvent of the mother liquor was evaporated *in vacuo*. The residue thus obtained was dissolved in chloroform, and washed with saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 3:1) to obtain 4 as white powder [441.2 mg (yield 55.7%)].

[0029] This product was further purified by HPLC using a reversed phase partition column (acetonitrile-water) to obtain β -anomer (**4B**) [248.16 mg (yield 32.3%)] and α -anomer (**4A**) [52.84 mg (yield 6.7%)], respectively, both as white powder.

35

Compound 4

[0030]

40 C₆₀H₆₃FO₁₄ MW = 1027.148

β -anomer (48)

〔0031〕

¹H-NMR [500 MHz, CDCl₃, Ref = 0.000 ppm (TMS)]
 1 : 5.040 (1H, d, J_{1,2} = 8.06)
 2 : 5.492 (1H, d, J_{2,3} = 9.89)
 3 : 5.884 (1H, t, J_{3,4} = 10.99)
 4 : 5.660 (1H, t)
 5 : 4.064 - 4.044 (1H, m)
 6 : 4.643 (2H, t)

55 $(\text{CH}_3\text{C}_6\text{H}_4\text{CO}) \times 4$: 2.405, 2.363, 2.351, 2.299
 (each 3H, s)
 $(\text{CH}_3\text{C}_6\text{H}_4\text{CO}) \times 4$: 7.873, 7.831, 7.808, 7.732
 (each 2H, d, $J = 6.9$ Hz)

IR ν ^{KBr} cm⁻¹ 3508(O-H), 1734(C=O position-20), 1665(C=O position-3)
 FAB(+)MS 1027(M+H)⁺, 1009(M-OH)⁺
 MP : 152 - 155°C

5 α -anomer (4 α)

[0032]

1 : 5.302 (1H, d, $J_{1,2}$ = 3.67)
 10 3 : 6.215 (1H, t)
 4 : 5.727 (1H, t)
 5 : 4.631 - 4.605 (1H, m)
 6 : 4.867 (1H, dd, $J_{6,6'}$ = 12.46)
 6': 4.276 (1H, dd)
 15 ($\text{CH}_3\text{C}_6\text{H}_4\text{CO-}$) x 4 : 2.410, 2.367, 2.348, 2.300
 (each 3H, s)
 ($\text{CH}_3\text{C}_6\text{H}_4\text{CO-}$) x 4 : 7.899, 7.864, 7.853, 7.768
 (each 2H, d)
 20 IR ν ^{KBr} cm⁻¹ 3438(O-H), 1731(C=O position-20), 1666(C=O position-3)
 FAB(+)MS 1027(M+H)⁺, 1009(M-OH)⁺
 MP : 150 - 153°C

25 4) Deprotection of glucosyldexamethasone (β -anomer)

[0033] 4 β (144 mg) was dissolved in methanol (16 ml), and to this solution was added, at 0 - 5°C, 1 M sodium methoxide (107.6 μ l). The resulting mixture was stirred for 5 h at room temperature. The reaction solution was applied to a gel filtration column of LH-20, and eluted with methanol. After the solvent of fractions containing product was distilled off *in vacuo*, the residue thus obtained was purified by HPLC using a reversed phase partition column (acetonitrile-water) to obtain 5 β as white powder [67.8 mg (yield 88.5%)].

Compound 5 β

35 [0034]

$\text{C}_{28}\text{H}_{39}\text{FO}_{10}$ MW = 554.608
¹H-NMR [(500 MHz, d6-DMSO, Ref = 2.50ppm(DMSO))]
 1 : 4.170 (1H, d, $J_{1,2}$ = 7.70)
 40 5 : 3.438 (1H, dd, $J_{5,6}$ = 12.09)
 6 : 3.696 (1H, dd, $J_{6,6'}$ = 1.83)
 FAB(-)MS 553(M-H)⁺
 MP : 238 - 241°C

45 5) Deprotection of glucosyldexamethasone (α -anomer)

[0035] 4 α (35 mg) was dissolved in methanol (10 ml), and to this solution was added 1 M sodium methoxide (62 μ l) at 0 - 5°C. The resulting mixture was stirred for 5 h at room temperature. The reaction mixture was loaded onto a gel filtration column of LH-20, and eluted with methanol. After the solvent of fractions containing product was distilled off *in vacuo*, the residue thus obtained was purified by HPLC using a reversed phase partition column (acetonitrile-water) to obtain 5 α as white powder [7.46 mg (yield 40.0%)].

Compound 5 α

55 [0036]

$\text{C}_{28}\text{H}_{39}\text{FO}_{10}$ MW = 554.608
 IR ν ^{KBr} cm⁻¹ 3404(O-H), 1712(C=O position-20), 1661(C=O position-3)

FAB(-)MS 553(M-H)⁺

MP : 173 - 176°C

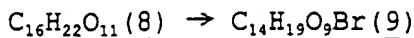
Example 2

5

Synthesis of glucosyldexamethasone (ortho ester)(Fig. 2)

1) Bromination of glucose (per Ac derivative)

10 [0037]



15

(MW = 390.34) (MW = 411.20)

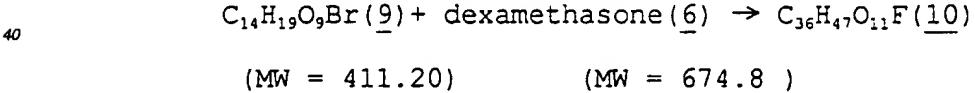
20 [0038] To hydrogen bromide-acetic acid solution (80 ml) pre-cooled to 0 - 5°C was added pentaacetyl- β -D-glucose (8) (20 g), and the mixture was stirred for 3 h at the same temperature. Then, after the solvent was distilled off *in vacuo*, the residue was dissolved in chloroform, and the solution was washed with saturated sodium bicarbonate solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was recrystallized from ethyl alcohol (60 ml) to obtain 9 as white powder [12.0 g (yield 56.7%)].

25 ¹H-NMR [500 MHz, CDCl₃, Ref = 0.000ppm(TMS)]

1 : 6.612 (1H, d, J_{1,2} = 4.03)
 2 : 4.842 (1H, dd, J_{2,3} = 9.89)
 3 : 5.562 (1H, t)
 4 : 5.163 (1H, t)
 5 : 4.292 (1H, dd, J_{5,6} = 4.03)
 6 : 4.332 (1H, dd, J_{6,6'} = 12.45)
 6' : 4.122 (1H, dd)
 (-OCOCH₃) x 4 : 2.103, 2.099, 2.082, 2.036 (each 3H, s)

35 2) Synthesis of glucosyldexamethasone (ortho ester)

[0039]



45

[0040] Dexamethasone (6) (1.7 g) was dissolved in chloroform (300 ml), and to this solution were added molecular sieve 4A (5 g) and silver carbonate (5.5 g). To this solution was added, under a nitrogen atmosphere, a glucose bromide (9, 5 g) dissolved in chloroform (150 ml), and the mixture was stirred for 4 h. After the reaction solution was filtered, the filtrate was washed with saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. The residue thus obtained was purified by silica gel column chromatography first with a solvent system (chloroform:methanol = 30:1), and then with another solvent system (toluene:ethyl acetate = 2:1) to obtain (10) as white powder [193.8 mg (yield 43.5%)].

55

Compound 10

[0041]

R_f = 0.56 (silica gel TLC, CHCl₃ : CH₃OH = 30 : 1)

¹H-NMR [500 MHz, CDCl₃, Ref = 0.000ppm(TMS)]
 1 : 5.786 (1H, d, J_{1,2} = 5.13)
 (-OCOCH₂) x 4 : 2.142, 2.115, 2.111 (12H, s)

5 Example 3

Synthesis of galactosyldexamethasone (Fig. 3)

10 1) Toluoylation of galactose (11 → 12)

[0042] D-(+)-galactose (11) (2 g) was dissolved in chloroform (40 ml), and to this solution were added *p*-toluoyl chloride (14.5 ml) and pyridine (8.9 ml) drop-wise at 0 - 5°C. While the reaction temperature was raised slowly to room temperature, the mixture was stirred for 5 h. After the reaction solution was poured into ice-water and extracted with chloroform, the organic layer was washed successively with saturated solutions of copper sulfate, sodium bicarbonate and sodium chloride. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. A portion (5 g) of the residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 40:1) to obtain 12 as white powder [2.4 g (yield 97.4%)].

15 Compound 12

20 [0043]

C₄₆H₄₂O₁₁ MW = 770.831
¹H-NMR [500 MHz, CDCl₃, Ref = 0.000ppm(TMS)]
 25 CH₃C₆H₄CO- : 8.000, 7.985, 7.837, 7.740, 7.696
 (each 2H, d, J = 8.43)
 CH₃C₆H₄CO- : 2.452, 2.449, 2.372, 2.305, 2.298
 (each 3H, S)

30 2) Bromination of 12 (12 → 13)

[0044] 12 (2.35 g) was dissolved in chloroform (10 ml), and to this solution was added hydrogen bromide-acetic acid solution (4.58 ml) at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred overnight. After removing the unreacted bromine with an argon stream, the solvent was distilled off *in vacuo*. The residue was taken up into chloroform, and washed with cold saturated sodium bicarbonate solution. After dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo* to obtain 13 as pale yellow powder [1.87 g (yield 83.7%)].

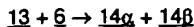
35 40 Compound 13

[0045]

45 C₃₈H₃₅O₉Br MW = 715.593
¹H-NMR [500 MHz, CDCl₃, Ref = 0.00ppm (TMS)]
 1 : 6.963 (1H, d, J_{1,2} = 4.03)
 2 : 5.614 (1H, dd, J_{2,3} = 10.63)
 3 : 6.018 (1H, dd, J_{3,4} = 3.29)
 4 : 6.068 (1H, dd)
 5 : 4.883 (1H, t)
 6 : 4.598 (1H, dd, J_{6,6'} = 11.72)
 6': 4.424 (1H, dd)

50 55 CH₃C₆H₄CO- : 7.946, 7.896, 7.880, 7.676
 7.278, 7.213, 7.185, 7.050
 (each 2H, d, J = 8.06)
 CH₃C₆H₄CO- : 2.444, 2.394, 2.360, 2.302
 (each 3H, s)

3) Synthesis of galactosylexamethasone



5 [0046] Dexamethasone 6 (456 mg) was dissolved in tetrahydrofuran (20 ml), and to this solution were added molecular sieve 5A (700 mg) and silver triflate (598 mg). To this solution was added, under an argon atmosphere, a galactose bromide 13 (1.7 g) dissolved in tetrahydrofuran (20 ml), and the mixture was stirred at room temperature for 2 - 3 h. After the reaction solution was filtered, the solvent was distilled off from the mother liquor *in vacuo*. The residue was dissolved in ethyl acetate, washed with saturated sodium chloride solution, and dried over anhydrous magnesium sulfate.

10 The solvent was distilled off *in vacuo*, and the residue thus obtained was first purified by silica gel chromatography (toluene:ethyl acetate = 3:1). The product was further purified by HPLC using a reversed phase partition column (acetonitrile:water) to obtain β -anomer (14 β) [232.2 mg (yield 31.2%)] and α -anomer (14 α) [178.6 mg (yield 24.0%)], both as white powder.

15 Compound 14

[0047]

20 $C_{60}H_{63}FO_{14}$ MW = 1027.148

 β -anomer (14 β)

[0048]

25 1H -NMR(500 MHz, $CDCl_3$, Ref = 0.00ppm (TMS))
 1 : 4.947 (1H, d, $J_{1,2} = 8.06$)
 2 : 5.829 (1H, dd, $J_{2,3} = 10.26$)
 3 : 5.572 (1H, dd, $J_{3,4} = 3.30$)
 4 : 5.906 (1H, d)

30 $CH_3C_6H_4CO-$: 7.991, 7.879, 7.876, 7.658, 7.292, 7.240,
 7.168, 7.040 (each 2H, d, $J = 8.06$)
 $CH_3C_6H_4CO-$: 2.426, 2.414, 2.346, 2.292
 (each 3H, s)

35 IR ν^{KBr} cm^{-1} 3496(O-H), 1731(C=O position-20), 1666(C=O position-3)
 FAB(+)MS 1027($M+H$)⁺, 1009($M-OH$)⁺
 MP : 163 - 165°C

40 α -anomer (14 α)

[0049]

45 1 : 5.438 (1H, d, $J_{1,2} = 3.66$)
 2 : 5.666 (1H, dd, $J_{2,3} = 10.26$)
 5 : 4.548 (1H, dd, $J_{5,6} = 5.13$,
 $J_{5,6'} = 7.69$)
 6 : 4.695 (1H, dd, $J_{6,6'} = 10.99$)
 6': 4.308 (1H, dd)

50 $CH_3C_6H_4CO-$: 8.002, 7.883, 7.835, 7.667, 7.295, 7.192,
 7.157, 7.015 (each 2H, d, $J = 8.06$)
 $CH_3C_6H_4CO-$: 2.457, 2.387, 2.341, 2.294
 (each 3H, s)

55 IR ν^{KBr} cm^{-1} 3460(O-H), 1730(C=O position-20), 1666(C=O position-3)
 FAB(+)MS 1027($M+H$)⁺, 1009($M-OH$)⁺
 MP : 163 - 165°C

4) Deprotection of galactosylexamethasone (β) (14 β \rightarrow 15 β)

[0050] 14 β (160 mg) was dissolved in methanol (15 ml), and to this solution was added 1 M sodium methoxide (121 μ l) at 0 - 5°C. The mixture was stirred for 3 h at room temperature. The reaction solution was loaded onto a gel filtration column of LH-20, and eluted with methanol. After the solvent was distilled off from fractions containing product *in vacuo*, the residue thus obtained was purified by HPLC using a reversed phase partition column (acetonitrile-water) to obtain 15 β as white powder [67.9 mg (yield 78.6%)].

Compound 15

[0051]

$C_{28}H_{39}FO_{10}$ MW = 554.608
 1H -NMR [(500 MHz, CD_3OD , Ref = 3.30ppm (CH_3OD))
 1 : 4.236 (1H, d, $J_{1,2} = 7.69$)
 2 : 3.593, 3.424 (1H, dd, $J_{2,3} = 9.89$)
 3 : 3.476, 3.456 (1H, dd, $J_{3,4} = 3.30$)
 4 : 3.795 (1H)
 5 : 3.505, 3.492 (1H, dd, $J_{5,6} = 6.96$, $J_{5,6} = 4.76$)
 6 : 3.774, 3.752 (1H, dd, $J_{6,6'} = 11.35$)
 6': 3.719, 3.697 (1H, dd)
 FAB(-)MS 553(M-H)⁺
 MP : 175 - 178°C

25 5) Deprotection of galactosylexamethasone (α) (14 α \rightarrow 15 α)

[0052] 14 α (127.05 mg) was dissolved in methanol (10 ml), and to this solution was added 1 M sodium methoxide (96 μ l) at 0 - 5°C. The mixture was stirred at room temperature for 3 h. The reaction mixture was applied to a gel filtration column of LH-20, and eluted with methanol. After the solvent was distilled off from fractions containing product *in vacuo*, the residue thus obtained was purified by HPLC using a reversed phase partition column (acetonitrile-water) to obtain 15 α as white powder [49.19 mg (yield 72.8%)].

Compound 15

35 [0053]

$C_{28}H_{39}FO_{10}$ MW = 554.608
 1H -NMR [(500 MHz, CD_3OD , Ref = 3.30ppm (CH_3OD))
 1 : 3.885 (1H, d, $J_{1,2} = 2.93$)
 2 - 6 : 3.6 - 3.8 ppm(6H, m)
 IR ν^{KBr} cm^{-1} 3438(O-H), 1715(C=O position-20), 1662(C=O position-3)
 FAB(-)MS 553(M+H)⁺
 MP : 225 - 228°C

45 Example 4

Synthesis of mannosylexamethasone (Fig. 4)

1) Toluoylation of mannose

[0054] D-(+)-Mannose 21 (2.3 g) was dissolved in chloroform (40 ml), and to this solution were added *p*-toluoyl chloride (14.5 ml) and pyridine (8.9 ml) drop-wise at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 5 h. The reaction solution was poured into ice-water, and extracted with chloroform. The organic layer was washed successively with saturated solutions of copper sulfate, sodium bicarbonate, and sodium chloride. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. A portion (6 g) of the residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 40:1) to give 22 as white powder [3.18 g (yield 88.7%)].

Compound 22

[0055]

5 $C_{46}H_{42}O_{11}$
 1H -NMR [500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

($CH_3C_6H_4CO-$) $\times 5$: 8.078, 7.961, 7.950, 7.834, 7.738, 7.345, 7.195, 7.178, 7.151, 7.077
(each 2H, d, J = 8.06)

10 ($CH_3C_6H_4CO-$) $\times 5$: 2.476, 2.449, 2.423, 2.350, 2.306
(each 3H, s)

Position-1 of mannose : 6.579 (1H, d, $J_{1,2}$ = 1.84)

2) Bromination of mannose derivative (22)

15 [0056] 22 (3.14 g) was dissolved in chloroform (15 ml), and to this solution was added hydrogen bromide-acetic acid solution (6.12 ml) at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred at room temperature overnight. After the unreacted bromine was removed with an argon stream, the solvent was distilled off *in vacuo*. The residue was dissolved in chloroform, and washed with cold saturated sodium bicarbonate solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo* to give 23 as light yellow powder [2.61 g (yield 87.6%)].

Compound 23

[0057]

25 $C_{38}H_{35}O_9Br$ MW = 715.593
 1H -NMR [500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

30 ($CH_3C_6H_4CO-$) $\times 4$: 7.972, 7.897, 7.858, 7.719
(each 2H, d, J = 8.06)

($CH_3C_6H_4CO-$) $\times 4$: 2.430, 2.359, 2.294
(12H, s)

35 3) Synthesis of mannosylexamethasone

40 [0058] Dexamethasone (6) (600 mg) was dissolved in tetrahydrofuran (20 ml), and to this solution were added molecular sieve 5A (600 mg) and silver triflate (783 mg). To this mixture was added, under an argon atmosphere, a mannose bromide 23 (2.3 g) dissolved in tetrahydrofuran (15 ml), and the reaction mixture was stirred for 4 h until the reaction temperature reached room temperature. The reaction solution was filtered, and the solvent of the mother liquor was distilled off *in vacuo*. The residue thus obtained was dissolved in ethyl acetate, washed with saturated sodium chloride solution, and then the organic layer was dried over anhydrous magnesium sulfate. After the solvent was distilled off *in vacuo*, the residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 3:1) to obtain 647 mg of white powder.

45 [0059] The above product was further purified by HPLC using a reversed phase partition column (acetonitrile-water) to obtain α -anomer (24 α) [462.3 mg (yield 29.2%)].

Compound 24 α

[0060]

50 $C_{60}H_{63}FO_{14}$ MW = 1027.148
 1H -NMR [500 MHz, $CDCl_3$, Ref = 0.000ppm (TMS)]

1 : 5.216 (1H, s)

55 2 : 5.954 (1H, dd, $J_{2,3}$ = 3.29)
3 : 6.153 (1H, dd, $J_{3,4}$ = 10.25)
6' : 4.456 (1H, dd, $J_{6,6'}$ = 12.09)

$(\text{CH}_3\text{C}_6\text{H}_4\text{CO}) \times 4$: 8.183, 8.099, 8.007, 7.935
(each 2H, d, $J = 8.06$)

$(\text{CH}_3\text{C}_6\text{H}_4\text{CO}) \times 4$: 2.646, 2.612, 2.577, 2.508
(each 3H, s)

5

IR ν KBr cm^{-1} 3498(O-H), 1730(C=O position-20), 1667(C=O position-3)
FAB(+)MS 1027(M+H)⁺, 1009(M-OH)⁺
MP : 155 - 158°C

10 4) Deprotection of mannosyldexamethasone (α)

[0061] 24 α (150 mg) was dissolved in methanol (10 ml), and to this solution was added 1 M sodium methoxide (113 μ l) at 0 - 5°C. The mixture was stirred at room temperature for 2 h. The reaction solution was applied to a gel filtration column of LH-20, and eluted with methanol. After evaporation of the solvent from fractions containing product *in vacuo*, the residue was purified by HPLC using a reversed phase partition column (acetonitrile-water) to obtain 25 α as white powder [57.67 mg (yield 72.3%)].

Compound 25 α

20 [0062]

$\text{C}_{28}\text{H}_{39}\text{FO}_{10}$ MW = 554.608
 $^1\text{H-NMR}$ [500 MHz, DMSO, Ref = 2.50ppm (DMSO)]

1 : 4.625 (1H, d, $J_{1,2} = 1.83$)
2 : 3.707 (1H, d, $J_{2,3} = 3.30$)
4 : 3.403 (1H)
6 : 3.647 (1H, dd, $J_{6,6'} = 11.73$)
IR ν KBr cm^{-1} 3438(O-H), 1715(C=O position-20), 1662(C=O position-3)
FAB(-)MS 553(M+H)⁺
MP : 189 - 192°C

5) Acetylation of mannose

[0063]

35



40

[0064] D-(+)-Mannose 21 (15 g) was suspended in acetic anhydride (180 ml), and to this suspension was added pyridine (46.5 ml) drop-wise at 0 - 5°C. The mixture was stirred at room temperature for about 5 h. The reaction solution was poured into ice-water, extracted with chloroform, and the organic layer was washed with 5% copper sulfate solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo* to give 27 as pale yellow oily product (36.9 g).

$^1\text{H-NMR}$ [500 MHz, CDCl_3 , Ref = 0.000ppm(TMS)]
1 : 6.091 (1H, d, $J_{1,2} = 1.83$)
6 : 4.332 (1H, dd, $J_{6,6'} = 12.46$)
6' : 4.122 (1H, dd, $J_{5,6'} = 2.57$)

$(-\text{OCOCH}_3) \times 5$: 2.181, 2.171, 2.096, 2.057, 2.011
(each 3H, s)

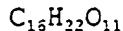
6) Bromination of mannose

[0065]

5

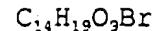
27

→

28

10

(MW = 390.34)



(MW = 411.20)

15 [0066] 27 (5.8 g) was dissolved in chloroform (11 ml), and to this solution was added a hydrobromide-acetic acid solution (11 ml) at 0 - 5°C. The mixture was stirred for about 4 h. The reaction solution was washed with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* gave 28 as pale yellow oily product [5.9 g (yield 95.9%)].

20 ¹H-NMR [500 MHz, CDCl₃, Ref = 0.000ppm(TMS)]
 1 : 6.298 (1H, d, J_{1,2} = 1.10)
 2 : 5.451 (1H, dd, J_{2,3} = 3.30)
 3 : 5.720 (1H, dd, J_{3,4} = 10.26)
 4 : 5.372 (1H, t)
 25 5 : 4.226 (1H, ddd, J_{5,6} = 4.76)
 6 : 4.332 (1H, dd, J_{6,6'} = 12.45)
 6' : 4.144 (1H, dd, J_{5,6'} = 2.20)
 (-OCOCH₃) x 4 : 2.178, 2.108, 2.077, 2.012 (each 3H, s)

30 7) Synthesis of mannosyldexamethasone (per Ac derivative)

[0067]

35 $C_{14}H_{19}O_9Br$ (28) + dexamethasone (6) → $C_{36}H_{47}FO_{14}$ (29)
 (MW = 411.20) (MW = 722.76)

40

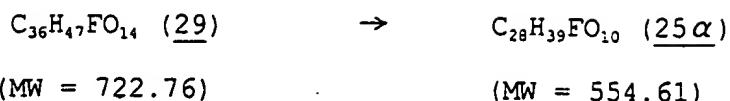
[0068] Dexamethasone 6 (1.7 g) was dissolved in chloroform (300 ml), and to this solution were added molecular sieve 4A (5 g) and silver carbonate (5.5 g). To this mixture was added, under a nitrogen atmosphere, a mannose bromide 28 (5.8 g) dissolved in chloroform (150 ml), and stirred at room temperature overnight. After the reaction solution was filtered, the mother liquor was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After the solvent was distilled off *in vacuo*, the residue thus obtained was purified by silica gel column chromatography first with (chloroform:methanol = 30:1) and further purified by the same system with (toluene:ethyl acetate = 2:1) to obtain 29 as white powder [453.7 mg (yield 49.6%)].

50 ¹H-NMR [500 MHz, CDCl₃, Ref = 0.000ppm(TMS)]
 1 : 5.529 (1H, d, J_{1,2} = 2.93)
 2 : 4.860 (1H, dd, J_{2,3} = 4.40)
 3 : 5.034 (1H, dd, J_{3,4} = 9.90)
 4 : 5.295 (1H, t, J_{4,5} = 9.52)
 5 : 3.709 (1H, ddd, J_{5,6} = 5.47)
 55 6 : 4.309 (1H, dd, J_{6,6'} = 12.45)
 6' : 4.122 (1H, dd, J_{5,6'} = 2.57)
 (-OCOCH₃) x 4 : 2.110, 2.077, 2.072, 1.801 (each 3H, s)
 FAB(+)MS 723(M+H)⁺

8) Deacetylation of mannosylexamethasone

[0069]

5



10

[0070] 5 (108.24 mg) was dissolved in methanol (25 ml), and to this solution was added 1 M sodium methoxide (1.25 ml) at 0 - 5°C. The mixture was stirred at room temperature for 6 h. The reaction solution was applied to a gel filtration column of LH-20 and eluted with methanol. The solvent was distilled off from fractions containing product *in vacuo* to give 25α as white powder [81.4 mg (yield 97.8%)].

Example 5

Synthesis of β-N-acetylglucosaminylexamethasone (Fig. 5)

20

1) Synthesis of N-acetylglucosaminyl chloride (31 → 33)

25

[0071] N-Acetylglucosamine 31 [10 g (45.2 mmol)] was suspended in acetyl chloride (20 ml), and stirred at room temperature overnight. The reaction solution was diluted with chloroform (100 ml), and poured into ice-water. The chloroform layer was washed with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and the solvent was distilled off *in vacuo*. The residue thus obtained was dissolved in diethyl ether (about 100 ml), and allowed to stand at -30°C overnight. Pale yellow powder (33) which precipitated was collected by filtration [12.7 g (yield 76.8%)].

Compound 33

30

[0072]

 $\text{C}_{14}\text{H}_{20}\text{ClNO}_8 \quad \text{MW} = 365.77$

MP : 123 - 126°C (decomp.)

35

FAB(+)MS 364(M-H)⁺, 366(M+H)⁺¹H-NMR (500 MHz, CDCl_3 , Ref = 0.000ppm(TMS))

δ: 1.991, 2.058, 2.060, 2.110 (each 3H, 3OAc+NHAc)

4.141 (1H, dd, $J = 1.8, 12.1\text{Hz}$, H-6)

40

4.307 -4.254 (2H, m, H-5,6)

4.538 (1H, ddd, $J = 3.7, 8.8, 10.6\text{Hz}$, H-2)5.221 (1H, t, $J = 9.9\text{ Hz}$, H-4)5.325 (1H, t, $J = 10.6\text{Hz}$, H-3)5.811 (1H, d, $J = 8.8\text{ Hz}$, NHAc)6.193 (1H, d, $J = 3.7\text{ Hz}$, H-1)45 IR $\nu_{\text{KBr}} \text{cm}^{-1}$: 3245(NH), 1742(OCOCH₃)1644(NHCOCH₃)

2) Synthesis of a protected derivative of N-acetylglucosaminylexamethasone

50

33 + dexamethasone (6) → 34

55

[0073] An N-acetylglucosamine chloride 33 [2.8 g (7.66 mmol)] and dexamethasone 6 [1.6 g (2.55 mmol)] were suspended in α-methylstyrene, and the suspension was stirred at 80 - 90°C for 5 h. The reaction solution was diluted with chloroform, filtered to remove insoluble materials, and the filtrate was evaporated to dryness *in vacuo*. The residue thus obtained was purified by silica gel column chromatography, eluted first with (chloroform:methanol = 20:1) and then with (toluene:ethyl acetate = 1:3) to give 34 as pale yellow powder [114.2 mg (yield 6.2%)]. The powder was dissolved in a small amount of ethyl acetate, and allowed to stand at -30°C for 3 days. Precipitated crystals were collected by fil-

tration, weighing 81.4 mg (white powder).

Compound 34

5 [0074]

$C_{36}H_{48}FNO_{13}$ MW = 721.77
 MP : 251°C
 FAB(+)MS 704 (M-H₂O)⁺, 722 (M+H)⁺,
 10 744 (M+Na)⁺
 IR ν^{KBr} cm⁻¹ : 3350(OH), 1750(OCOCH₃)
 1730, 1662(C=O), 1620, 1603(C=C)
 15 ¹H-NMR (500 MHz, CDCl₃, Ref = 0.000ppm(TMS))
 δ : 0.883 (3H, d, J = 7.3 Hz, 16-CH₃)
 0.964 (3 H, s, CH₃)
 1.560 (3 H, s, CH₃)
 20 1.949, 2.041, 2.043, 2.106 (3H, 4s, 3OAc+NHAc)
 3.713 (1H, ddd, J = 2.9, 4.8, 9.5 Hz, H-5_{GlcNAc})
 3.818 (1H, dd, J = 8.4, 10.3Hz, H-2_{GlcNAc})
 4.160 (1H, dd, J = 2.9, 12.1Hz, H-6_{GlcNAc})
 4.329 (1H, dd, J = 4.8, 12.1Hz, H' -6_{GlcNAc})
 25 4.480 (1H, d, J = 18.0Hz, H-21)
 4.735 (1H, d, J = 18.0Hz, H' -21)
 4.840 (1H, d, J = 8.4 Hz, H-1_{GlcNAc})
 5.046 (1H, t, J = 9.5 Hz, H-4_{GlcNAc})
 30 5.304 (1H, dd, J = 9.5, 10.3Hz, H-3_{GlcNAc})
 6.116 (1H, s, H-4)
 6.340 (1H, dd, J = 1.8, 9.9 Hz, H-1)
 7.283 (1H, d, J = 9.9 Hz, H-2)

3) Synthesis of a deprotected derivative of N-acetylglucosaminylexamethasone

35

34 → 35β

[0075] A protected derivative of N-acetylglucosaminylexamethasone 34 [56.0 mg (77.6 μmol)] was suspended in methanol (1 ml), and to this suspension was added 1 M sodium methoxide (16 μl) at room temperature. The mixture
 40 was stirred at room temperature for 50 min. The reaction solution which turned yellow was applied to a gel filtration column of LH-20, and eluted with methanol. Evaporation of the solvent was distilled off from fractions containing product *in vacuo* to give 35β as white powder [46.6 mg (yield 100%)].

Compound 35β

45

[0076]

$C_{30}H_{42}FNO_{10}$ MW = 595.66
 MP : 208 - 211°C (decomp.)
 50 FAB(+)MS 596 (M+H)⁺, 618 (M+Na)⁺
 IR ν^{KBr} cm⁻¹ : 3420(OH), 1718, 1660(C=O),
 1620 (C=C)
 55 ¹H-NMR [500 MHz, CD₃CN, Ref = 1.950ppm(CH₃CN)]
 δ : 0.832 (3H, d, J = 7.3 Hz, 16-CH₃)
 0.949 (3H, s, CH₃)

1.530 (3H, s, CH₃)
 3.214 - 3.270 (2H, m, H-4_{GlcNAc}+ H-5_{GlcNAc})
 3.400 (1H, dd, J = 8.1, 9.9 Hz, H-3_{GlcNAc})
 3.548 (1H, dd, J = 8.4, 9.9 Hz, H-2_{GlcNAc})
 3.596 (1H, dd, J = 6.2, 12.1 Hz, H-6_{GlcNAc})
 3.816 (1H, dd, J = 1.5, 12.1 Hz, H'-6_{GlcNAc})
 4.383 (1H, d, J = 8.4 Hz, H-1_{GlcNAc})
 6.029 (1H, s, H-4)
 6.239 (1H, dd, J = 1.8, 10.3 Hz, H-1)
 7.284 (1H, d, J = 10.3 Hz, H-2)

Example 6

Synthesis of N-acetylgalactosaminylxexamethasone (Fig. 6)

15 1) Synthesis of a protected derivative of N-acetylgalactosaminylxexamethasone

[0077]

20

41 → 4343 + 6 → 44α + 44β

25

[0078] N-Acetylgalactosamine 41 [3.0 g (13.56 mmol)] was suspended in acetyl chloride (6 ml), and stirred at room temperature overnight. The reaction mixture was diluted with chloroform (24 ml), poured into ice-water, and the chloroform layer was washed with saturated sodium bicarbonate. The organic layer dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo* to give an N-acetylgalactosamine chloride 43 (4.35 g). To a mixture of dexamethasone 6 [5.95 g (15.17 mmol)], the N-acetylgalactosamine chloride 43 [5.55 g (15.17 mmol)], trityl chloride [4.23 g (15.17 mmol)] and zinc chloride [2.07 g (15.17 mmol)] was added nitromethane (130 ml), and the resulting mixture was stirred under an argon atmosphere at room temperature overnight. The reaction solution was diluted with chloroform, and filtered to remove insoluble materials. The filtrate was washed successively with saturated solutions of sodium bicarbonate and sodium chloride. After drying the organic layer over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*, and the residue thus obtained was purified by silica gel column chromatography (acetone:toluene = 2:3) to give fractions containing the desired product (950.8 mg). This fraction was further purified by HPLC using a reversed phase partition column (acetonitrile-water) to give α-anomer 44α [98.0 mg (yield 0.9%)] and β-anomer 44β [569.5 mg (yield 5.2%)], respectively, both as white powder.

40

Compound 44α

[0079]

45 C₃₆H₄₈FNO₁₄ MW = 721.77
 MP : 165 - 167°C
 FAB(+)MS ; 722(M+H)⁺
 IR ν_{max}^{KBr} cm⁻¹ : 3440(O-H), 1755(COCH₃), 1669(C=O), 1620(C=C)
¹H-NMR [500 MHz, CDCl₃, Ref = 0.000ppm(TMS)]

50

δ : 0.917(3H, d, J_{16CH₃,16} = 7.3, 16-CH₃)
 1.014(3H, s, H-18)
 1.565(3H, s, H-19)
 1.997, 2.008, 2.092, 2.196(3H x 4, each s, COCH₃ x 4)
 3.918(1H, dd, J_{5',6} = 11.0, J_{5',5} = 8.8, H-6'_{GlcNAc})
 4.066(1H, dd, J_{5',6} = 5.1, H-5'_{GlcNAc})
 4.350(1H, dd, H-6'_{GlcNAc})
 4.498(1H, d, J_{gem} = 18.7, H-21')

4.547(1H, d, H-21)
 4.623(1H, *ddd*, $J_{2,1} = 3.7$, $J_{2,\text{NH}} = 9.9$, $J_{2,3} = 11.4$, H-2_{GalNAc})
 4.849(1H, d, H-1_{GalNAc})
 5.256(1H, *dd*, $J_{3,4} = 2.9$, H-3_{GalNAc})
 5.383(1H, d, H-4_{GalNAc})
 6.113(1H, d, $J_{4,1} = 2.2$, H-4)
 6.325(1H, *dd*, $J_{1,2} = 9.9$, H-1)
 6.480(1H, d, NHAc)
 7.235(1H, d, H-2)

10 Compound 44B

[0080]

15 $\text{C}_{36}\text{H}_{48}\text{FNO}_{14}$ MW = 721.77
 MP : 174 - 177°C (decomp.)
 FAB(+)-MS : 722(M+H)⁺, 744(M+Na)⁺

20 IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹ : 3450(O-H), 1750(COCH₃), 1660(C=O position-3),
 1622 and 1604(C=C)

¹H-NMR [500 MHz, CDCl₃, Ref = 0.000ppm(TMS)]

25 δ : 0.903(3H, d, $J_{16\text{CH}_3,16} = 7.3$, 16-CH₃)
 0.993(3H, s, H-18)
 1.564(3H, s, H-19)
 2.000, 2.012, 2.090, 2.186 (3H x 4, each s, COCH₃ x 4)
 3.850(1H, *dd*, $J_{5,6} = 5.9$, $J_{5,6} = 7.0$, H-5_{GalNAc})
 3.978(1H, *dd*, $J_{6,6} = 11.0$, H-6_{GalNAc})
 4.108(1H, *ddd*, $J_{2,1} = 8.4$, $J_{2,\text{NH}} = 8.8$, $J_{2,3} = 11.0$, H-2_{GalNAc})
 4.383(1H, *dd*, H-6_{GalNAc})
 4.630(1H, d, $J_{\text{gem}} = 18.3$, H-21)
 4.677(1H, d, H-1_{GalNAc})
 4.682(1H, d, H-21)
 5.174(1H, *dd*, $J_{3,4} = 3.3$, H-3_{GalNAc})
 5.338(1H, d, H-4_{GalNAc})
 6.070(1H, d, NHAc)
 6.112(1H, d, $J_{4,1} = 1.8$, H-4)
 6.328(1H, *dd*, $J_{1,2} = 9.9$, H-1)
 7.235(1H, d, H-2)

2) Synthesis of a deprotected derivative of N-acetylgalactosaminyldexamethasone (α)

44 α →45 α

45 [0081] A protected derivative of N-acetylgalactosaminyldexamethasone (α -anomer) 44 α [70.0 mg (0.097 mmol)] was dissolved in methanol (3 ml), and to this solution was added 1 M CH₃ONa/MeOH (0.1 ml). The mixture was stirred at room temperature for 3 h. The reaction solution was applied to a gel filtration column of LH-20, eluted with methanol, and the solvent of fractions containing product was evaporated *in vacuo* to give 45 α as white powder [54.9 mg (yield 95.0%)].

Compound 45 α

[0082]

55 $\text{C}_{30}\text{H}_{42}\text{FNO}_{10}$ MW = 595.66
 MP : 189 - 191°C
 FAB(+)-MS : 596(M+H)⁺, 618(M+Na)⁺

IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3426(O-H, 1715(C=O 20-position), 1665(C=O 3-position), 1620 and 1605(C=C)
 $^1\text{H-NMR}$ [500 MHz, CD_3OD , Ref = 0.000ppm(TMS)]

5 δ : 0.864(3H, d, $J_{16\text{CH}_3,16} = 7.3$, 16- CH_3)
 1.008(3H, s, H-18)
 1.583(3H, s, H-19)
 2.018(3H, s, COCH_3)
 3.692 - 3.721 (1H, m, H-6'_{GalNAc})
 3.748 - 3.778 (2H, m, H-5_{GalNAc}, H-6_{GalNAc})
10 3.819(1H, dd, $J_{3,2} = 11.0$, $J_{3,4} = 2.9$, H-3_{GalNAc})
 3.888(1H, d, H-4_{GalNAc})
 4.316(1H, dd, $J_{2,1} = 3.7$, H-2_{GalNAc})
 4.527(1H, d, $J_{\text{gem}} = 18.7$, H-21)
 4.580(1H, d, H-21)
15 4.801(1H, d, H-1_{GalNAc})
 6.076(1H, d, $J_{4,1} = 1.8$, H-4)
 6.283(1H, dd, $J_{1,2} = 10.3$, H-1)
 7.395(1H, d, H-2)

20 3) Synthesis of a deprotected derivative of N-acetylgalactosaminyldexamethasone (β)

44 β → 45 β

25 [0083] A protected derivative of N-acetylgalactosaminyldexamethasone (β) 44 β [84.5 mg (0.117 mmol)] was dissolved in methanol (0.5 ml), and to this solution was added 1 M $\text{CH}_3\text{ONa}/\text{MeOH}$ (24 μl), and the mixture was stirred at room temperature for 3 h. The reaction solution was applied to a gel filtration column, eluted with methanol, and the solvent of fractions containing product was evaporated *in vacuo* to give 45 β [63.9 mg (yield 91.7%)] as white powder.

Compound 45 β

30 [0084]

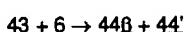
$\text{C}_{30}\text{H}_{42}\text{FNO}_{10}$ MW = 595.66

MP : 201 - 203°C

35 FAB(+)-MS ; 596($\text{M}+\text{H}$)⁺, 618($\text{M}+\text{Na}$)⁺
 IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3420(O-H), 1720(C=O position-20), 1660(C=O position-3), 1620 and 1602(C=C)
 $^1\text{H-NMR}$ [500 MHz, CD_3OD , Ref = 3.300ppm(CH_3OD)]

40 δ : 0.845(3H, d, $J_{16\text{CH}_3,16} = 7.3$, 16- CH_3)
 0.986(3H, s, H-18)
 1.575(3H, s, H-19)
 2.018(3H, s, COCH_3)
 3.472(1H, dd, $J_{5,6} = 7.3$, $J_{5,6'} = 4.8$, H-5'_{GalNAc})
 3.636(1H, dd, $J_{3,2} = 10.6$, $J_{3,4} = 2.9$, H-3_{GalNAc})
45 3.726(1H, dd, $J_{6',6} = 11.4$, H-6'_{GalNAc})
 3.797(1H, d, H-4_{GalNAc})
 3.806(1H, dd, H-6_{GalNAc})
 3.912(1H, dd, $J_{2,1} = 8.4$, H-2_{GalNAc})
 4.441(1H, d, H-1_{GalNAc})
50 4.593(1H, d, $J_{\text{gem}} = 18.3$, H-21)
 4.702(1H, d, H-21)
 6.069(1H, d, $J_{4,1} = 1.8$, H-4)
 6.277(1H, dd, $J_{1,2} = 10.3$, H-1)
 7.396(1H, d, H-2)

55 4) N-Acetylgalactosaminyldexamethasone (modified method)



[0085] An N-acetylgalactosamine chloride (43) (2.8 g) and dexamethasone (6) [1.00 g (2.55 mmol)] were suspended in α -methylstyrene, and stirred at 70°C for 4.5 h. The reaction solution was diluted with chloroform, filtered to remove insoluble materials, and the solvent of the filtrate was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (chloroform:methanol = 20:1) to give fractions containing β -anomer (281.0 mg) and those containing oxazoline derivative (365.3 mg), respectively. The β -anomer containing fraction was further purified by silica gel column chromatography (ethyl acetate) to obtain pale yellow powder 44 β [157.7 mg (yield 8.6%)], which was recrystallized from ethyl acetate (1 ml) to yield white powder (153.8 mg). The oxazoline derivative containing fraction was similarly purified by silica gel chromatography (ethyl acetate) to give an oxazoline derivative (44) as white powder [184.8 mg (yield 10.0%)].

10 Compound 44' (oxazoline derivative)

[0086]

15 $C_{36}H_{48}FN_{14}$ MW = 721.77
MP : 213 - 215°C (decomp.)
FAB(+)-MS : 722(M+H)⁺, 744 (M+Na)⁺

20 $\text{IR}_{\text{v}}^{\text{KBr}} \text{ cm}^{-1}$: 3400(O-H), 1750(COCH₃), 1722(C=O position-20),
1660(C=O position-3), 1618 and 1602(C=C)

¹H-NMR [500MHz, CDCl₃, Ref = 0.000ppm(TMS)]

25 δ : 0.917(3H, d, J_{16CH₃,16} = 7.0, 16-CH₃)
1.080(3H, s, H-18)
1.562(3H, s, H-19)
2.019, 2.089, 2.123, 2.149 (3H x 4, each s, COCH₃ x 4)
4.225(1H, dd, J_{6',6} = 11.4, J_{6',5} = 6.6, H-6'_{GalNAc})
4.250(1H, dd, J_{6',5} = 4.4, H-6'_{GalNAc})
30 4.312(1H, ddd, J_{2,1} = 1.1, J_{2,NH} = 6.6, J_{2,3} = 3.7, H-2_{GalNAc})
4.418(1H, dd, J_{4,3} = 6.2, J_{4,5} = 3.7, H-4_{GalNAc})
4.427(1H, d, J_{gem} = 17.2, H-21)
4.515(1H, d, H-21)
4.787(1H, dd, H-3_{GalNAc})
35 5.064(1H, d, H-1_{GalNAc})
5.424 - 5.454 (1H, m, H-5_{GalNAc})
6.111(1H, d, J_{4,1} = 1.8, H-4)
6.159(1H, d, NHAc)
6.333(1H, dd, J_{1,2} = 10.3, H-1)
40 7.261(1H, d, H-2)

5) Synthesis of a deprotected oxazoline derivative of N-acetylgalactosaminyldexamethasone

44' → 45'

45 [0087] A protected oxazoline derivative of N-acetylgalactosaminyldexamethasone (44') [89.0 mg (0.123 mmol)] was dissolved in methanol (1 ml), and to this solution was added 1 M CH₃ONa/MeOH (25 μ l). The resulting mixture was stirred at room temperature for 2 h. The reaction solution was applied to a gel filtration column of LH-20, and eluted with methanol. The solvent of fractions containing product were evaporated *in vacuo* to give 45' as white powder [67.9 mg (yield 92.7%)].

Compound 45' (oxazoline derivative)

[0088]

55 $C_{30}H_{42}FN_{10}$ MW = 595.66
MP : 169 - 172°C
FAB(+)-MS : 596(M+H)⁺, 618(M+Na)⁺

$^1\text{H-NMR}$ [500MHz, CD_3OD , Ref = 3.300ppm(CH_3OD)]

5	δ : 0.853(3H, d, $J_{16\text{CH}_3,16} = 7.3$, 16-CH_3) 1.006(3H, s, H-18) 1.579(3H, s, H-19) 1.960(3H, s, COCH_3) 3.601(2H, d, $J_{6,5} = 6.6$, $H\text{-6}_{\text{GalNAc}}$) 3.745(1H, dd, $J_{5,4} = 2.6$, $H\text{-5}_{\text{GalNAc}}$) 4.027(1H, d, $J_{4,3} = 5.9$, $H\text{-4}_{\text{GalNAc}}$) 4.058(1H, dd, $J_{3,2} = 3.7$, $H\text{-3}_{\text{GalNAc}}$) 4.228(1H, d, $H\text{-2}_{\text{GalNAc}}$) 4.383(1H, d, $J_{\text{gem}} = 18.3$, H-21) 4.693(1H, d, H-21) 4.950(1H, s, $H\text{-1}_{\text{GalNAc}}$) 6.070(1H, d, $J_{4,1} = 1.8$, H-4) 6.278(1H, dd, $J_{1,2} = 9.9$, H-1) 7.400(1H, d, H-2)
10	
15	

20 Example 7

Synthesis of β -glucuronyldexamethasone and toluoyl-protected derivative of β -glucuronyldexamethasone (Fig. 7)

1. Synthesis of β -glucuronyldexamethasone

[0089] 1) D-Glucuronolactone 51 (6.30 g) was suspended in methanol (100 ml), and to this suspension was added sodium hydroxide (12.6 mg). The compounds were completely solubilized by ultrasonic action. After the solvent was distilled off from the mixture *in vacuo*, pyridine (6.0 ml) and acetic anhydride (12.0 ml) were added to the residue under ice-cooling. While the reaction temperature was slowly raised to room temperature, the resulting mixture was continuously stirred for 12 h. Under ice-cooling, methanol was added to the reaction mixture to precipitate 52 as white powder, which was collected by filtration [5.69 g (yield 42.3%)].



40

100001

45 MW : C₁₅H₂₀O₁₁ = 376.14
MP : 182 - 183°C
ED-MS : m/z = 376 (M)⁺

IR ν KBr cm^{-1} : 1763(C=O), 1374(CH₃), 1231, 1208(C-C(=O)-O)

¹H-NMR (ppm, 500 MHz, CDCl₃, Ref = 0.000ppm(TMS))

55	1	5.770 (1H, d, $J_{1,2} = 7.70\text{Hz}$)
	2	5.146 (1H, dd, $J_{2,1} = 7.70, J_{2,3} = 9.16$)
	3	5.311 (1H, t, $J_{3,2} = J_{3,4} = 9.16$)
	4	5.250 (1H, t, $J_{4,3} = 9.16, J_{4,5} = 9.52$)
	5	4.181 (1H, d, $J_{5,4} = 9.52$)

-COOCH_3 3.747 (3H, s)
 -COCH_3 2.118, 2.031 (3H, s) x 2
 -COCH_3 2.039 (6H, s)

5 2) 52 (2.26 g) was dissolved in dichloromethane (20 ml) was added, and to this solution, under ice-cooling, a hydrobromide-acetic acid solution (10.0 ml). The mixture was stirred at room temperature for 12 h. After the reaction solution was washed with saturated sodium bicarbonate solution, the organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 4:1) to give 53 as white powder [1.57 g (yield 65.8%)].

10 52 \rightarrow 53

Compound 53

15 [0091]

MW : $\text{C}_{13}\text{H}_{17}\text{O}_9\text{Br} = 397.17$
 MP : 111 - 113°C
 FAB(+)MS : m/z = 397, 399 ($\text{M}+\text{H}$)⁺,

20 IR ν^{KBr} cm^{-1} : 1767, 1750(C=O), 1379(CH₃),
 1252, 1229, 1215(C-C(=O)-O)

25 ¹H-NMR (ppm, 500 MHz, CDCl_3 , Ref = 0.000ppm(TMS))
 1 6.643 (1H, d, $J_{1,2} = 4.03\text{Hz}$)
 2 4.859 (1H, dd, $J_{2,1} = 4.03$, $J_{2,3} = 9.89$)
 3 5.616 (1H, t, $J_{3,2} = 9.89$, $J_{3,4} = 9.52$)
 4 5.246 (1H, dd, $J_{4,3} = 9.52$, $J_{4,5} = 10.62$)
 30 5 4.584 (1H, d, $J_{5,4} = 10.62$)
 -COOCH_3 3.766 (3H, s)
 -COCH_3 2.100, 2.056, 2.052 (3H, s) x 3

35 [0092] 3) Dexamethasone 6 (1.54 g) was suspended in chloroform (150 ml), and to this solution were added, under an argon atmosphere, molecular sieve 4A (1.50 g) and silver carbonate (1.60 g) and 53 (1.53 g). The resulting mixture was stirred at room temperature for 4 days. After the reaction solution was filtered, the solvent of the filtrate was evaporated *in vacuo* to give crude 54' (2.80 g). Purification of the crude 54' (580 mg) by silica gel column chromatography (toluene:ethyl acetate = 2:1 \rightarrow 1:1) gave 54' as white powder [220.6 mg (yield 38.0%)].

40 53 + 6 \rightarrow 54'

Compound 54'

[0093]

45 MW $\text{C}_{35}\text{H}_{45}\text{O}_{14}\text{F} = 708.73$
 MP : 133 - 135°C
 FAB(+)MS : m/z = 709 ($\text{M}+\text{H}$)⁺, 731 ($\text{M}+\text{Na}$)⁺

50 IR ν^{KBr} cm^{-1} : 3396(O-H), 2944 (C-H),
 1757, 1665(C=O),
 1222(C-C(=O)-O)

55 ¹H-NMR (ppm, 500 MHz, CDCl_3 , Ref = 0.000ppm(TMS))
 1 5.863 (1H, d, $J_{1,2} = 5.13\text{Hz}$)
 2 4.253 (1H, dd, $J_{2,1} = 5.13$, $J_{2,3} = 2.57$)
 3 5.154 (1H, dd, $J_{3,2} = J_{3,4} = 2.57$)

4	5.191 (1H, dd, $J_{4,3} = 2.57$, $J_{4,5} = 8.42$)
5	4.256 (1H, d, $J_{5,4} = 8.42$)
-COOCH ₃	3.788 (3H, s)
-COCH ₃	2.129, 2.121 (3H, s) x 2
5 CH ₃ (ortho ester)	1.754 (3H, s)

[0094] 4) 54' (441.4 mg) was dissolved in acetonitrile/water mixture [140 ml(4/96, containing 0.1% TFA)], and this solution was applied in 20 ml portions to a HPLC column [μ -Bondasphere C₁₈-100 Å, flow-rate 23.0 ml/min, detection wave length 254 nm (UV), eluent A/B = water/95% acetonitrile (both containing 0.1% TFA) = 94/6 \rightarrow 80/20 \rightarrow 38/62], and eluted with the gradient for 30 min). Fractions containing product were evaporated *in vacuo*, and then lyophilized to give 54B as white powder [41.4 mg (yield 9.40%)].

54' \rightarrow 54B

15 Compound 54B

[0095]

20	MW : C ₃₅ H ₄₅ O ₁₄ F = 708.73
MP : 140 - 142°C	
FAB(+)MS : m/z = 709 (M+H) ⁺ , 731 (M+Na) ⁺	
IR ν ^{KBr} cm ⁻¹ :	3414(O-H), 2946 (C-H),
	1759, 1664(C=O),
25	1222(C-C(=O)-O)

¹H-NMR (ppm, 500 MHz, CDCl₃, Ref = 0.000ppm(TMS))

30	1 4.844 (1H, d, $J_{1,2} = 7.70$ Hz)
2	5.066 (1H, dd, $J_{2,1} = 7.70$, $J_{2,3} = 9.52$)
3	5.293 (1H, t, $J_{3,2} = J_{3,4} = 9.52$)
4	5.213 (1H, t, $J_{4,3} = J_{4,5} = 9.52$)
5	4.037 (1H, d, $J_{5,4} = 9.52$)
-COOCH ₃	3.767 (3H, s)
-COCH ₃	2.092, 2.038, 2.027 (3H, s) x 3

[0096] 5) 54' (823.1 mg) was dissolved in methanol (10 ml), and to this solution was added 1 M sodium methoxide (0.3 ml) at 0°C. The mixture was stirred at room temperature for 3 h. To this mixture were further added water (1 ml) and 1 M sodium methoxide (0.3 ml), and the resulting mixture was stirred at room temperature for 2 h. After the solvent of the reaction solution was evaporated *in vacuo*, water (10 ml) was added to the residue, and the mixture was filtered. The filtrate was lyophilized to give crude 55B (580.0 mg). This crude product was purified by HPLC under similar conditions as in 4). Fractions containing the product were evaporated *in vacuo*, and then lyophilized to give 55B as white powder [54.5 mg (yield 8.2%)].

45 54' \rightarrow 55B

Compound 55B

[0097]

50	MW : C ₂₈ H ₃₇ O ₁₁ F = 568.59
MP : 188 - 190°C	
FAB(+)MS : m/z = 569 (M+H) ⁺ , 591 (M+Na) ⁺	
55	IR ν ^{KBr} cm ⁻¹ : 3410(O-H), 2938 (C-H), 1716, 1662(C=O), 1607(C-C)

¹H-NMR ppm, 500 MHz (CD₃OD, Ref = 3.300ppm(CH₃OD))

1 4.523 (1H, d, $J_{1,2} = 7.74$ Hz)
 2 3.482 (1H, dd, $J_{2,1} = 7.74$, $J_{2,3} = 9.29$)
 3 3.554 (1H, t, $J_{3,2} = J_{3,4} = 9.29$)
 4 3.702 (1H, t, $J_{4,3} = 9.29$, $J_{4,5} = 9.51$)
 5 3.954 (1H, d, $J_{5,4} = 9.73$)

2. Synthesis of a toluoyl-protected derivative of β -glucuronidexamethasone (toluoyl derivative)

[0098] 1) D-Glucuronolactone **51** (4.86 g) was suspended in methanol (100 ml), and to this suspension was added sodium hydroxide (9.8 mg). The compounds were completely solubilized by ultrasonic action. After the solvent of the reaction solution was evaporated *in vacuo*, pyridine (50 ml), *p*-toluoyl chloride and chloroform (20 ml) were added to the residue under ice-cooling, and, while the reaction temperature was slowly raised to room temperature, the mixture was stirred for 12 h. Water was added to the reaction mixture under ice-cooling, and the chloroform layer was washed successively with water, and saturated solutions of sodium bicarbonate and copper sulfate. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 30/1 → 20/1) to give white powder [14.7 g (yield 78.2%)] consisting of **57 α** and **57 β** in a ratio of 1:1.5.

51 → 57

20 Compound **57**

[0099]

25 **57 α** MW : $C_{39}H_{36}O_{11}$ = 680.706
 MP : 83 - 85°C
 FAB(-)MS : m/z = 679 (M-H)⁺

30 IR ν ^{KBr} cm⁻¹ : 1736, 1613(C=O)
 1265(C-C(=O)-O)
 1100(O-C-C)

¹H-NMR (ppm, 500 MHz, CDCl₃, Ref = 0.000ppm(TMS))

35 1 6.874 (1H, d, $J_{1,2} = 3.66$ Hz)
 2 5.654 (1H, dd, $J_{2,1} = 3.66$, $J_{2,3} = 9.89$)
 3 6.280 (1H, t, $J_{3,2} = J_{3,4} = 9.89$)
 4 5.721 (1H, t, $J_{4,3} = J_{4,5} = 9.89$)
 5 4.727 (1H, d, $J_{5,4} = 9.89$)
 -COOCH₃ 3.669 (3H, s)
 -C₆H₄CH₃ 2.461, 2.372, 2.310, 2.304 (3H, s) x 4
 -C₆H₄CH₃ 8.028, 7.866, 7.792, 7.754, 7.327, 7.191, 7.118, 7.084 (2H, d, J = 8.06) x 8

45 **57 β** MW : $C_{39}H_{36}O_{11}$ = 680.706
 MP : 92 - 95°C
 FAB(-)MS : m/z = 679 (M-H)⁺

50 IR ν ^{KBr} cm⁻¹ : 1734, 1613(C=O)
 1266(C-C(=O)-O)
 1094(O-C-C)

¹H-NMR (ppm, 500 MHz, CDCl₃, Ref = 0.000ppm(TMS))

55 1 6.627 (1H, d, $J_{1,2} = 7.33$ Hz)
 2 5.794 (1H, dd, $J_{2,1} = 7.33$, $J_{2,3} = 8.79$)
 3 5.970 (1H, t, $J_{3,2} = J_{3,4} = 8.79$)

4	5.767 (1H, t, $J_{4,3} = J_{4,5} = 8.79$)
5	4.568 (1H, d, $J_{5,4} = 8.79$)
-COOCH ₃	3.606 (3H, s)
-C ₆ H ₄ CH ₃	2.377, 2.326 (6H, s) x 4
-C ₆ H ₄ CH ₃	7.909, 7.850, 7.127, 7.116 (2H, d, $J = 8.06$) x 4 7.797, 7.185 (4H, d, $J = 8.06$) x 2

[0100] 2) 57 (6.22 g) was dissolved in dichloromethane (100 ml), and to this solution was added, under ice-cooling, a hydrobromide-acetic acid solution (40 ml). The mixture was stirred at room temperature for 12 h. After the reaction solution was washed with saturated sodium bicarbonate solution, the organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated *in vacuo* to give 58 as white powder [5.54 g (yield 96.3%)].

57 → 58

15 Compound 58

[0101]

MW : C₃₁H₂₉O₉Br = 625.468
20 MP : 83 - 84°C
FAB(+)MS : m/z = 625, 627 (M+H)⁺

IR_v^{KBr} cm⁻¹ : 1733, 1613(C=O)
25 1266(C-C(=O)-O)
1106(O-C-C)

¹H-NMR (ppm, 500 MHz, CDCl₃, Ref = 0.000ppm(TMS))

1	6.884 (1H, d, $J_{1,2} = 4.03$ Hz)
2	5.308 (1H, dd, $J_{2,1} = 4.03$, $J_{2,3} = 9.89$)
3	6.241 (1H, t, $J_{3,2} = J_{3,4} = 9.89$)
4	5.692 (1H, t, $J_{4,3} = J_{4,5} = 9.89$)
5	4.835 (1H, d, $J_{5,4} = 9.89$)
-COOCH ₃	3.677 (3H, s)
-C ₆ H ₄ CH ₃	2.370, 2.358, 2.299 (3H, s) x 3
-C ₆ H ₄ CH ₃	7.872, 7.864, 7.784, 7.196, 7.186, 7.107 (2H, d, $J = 8.06$) x 6

[0102] 3) Dexamethasone 6 (0.94 g) was dissolved in dehydrated tetrahydrofuran (100 ml), and to this solution were added, under an argon atmosphere, molecular sieve 5A (1.0 g) and 58 (1.98 g). To the resulting mixture was added, under ice-cooling, a solution (0.6 ml) of silver triflate (1.27 g) and tetramethylurea in dehydrated tetrahydrofuran, and, while the reaction temperature was slowly raised to room temperature, the resulting mixture was stirred for 1 h. After the reaction solution was filtered, the solvent was evaporated from the filtrate *in vacuo*, and the residue thus obtained was taken up in ethyl acetate (200 ml). After this solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (chloroform:methanol = 60/1) followed by HPLC (column μ -Bondasphere C₁₈-100 Å, flow rate 23.0 ml/min, detection wavelength 254 nm (UV), eluent A/B = water/95% acetonitrile (both containing 0.1% TFA) = 30/70 → 0/100, eluted with the gradient 30 min). Fractions containing product were evaporated *in vacuo*, and then lyophilized to give 59 α [50.0 mg (yield 2.2%)] and 59 β [163.3 mg (yield 7.3%)], both as white powder.

50 58 + 6 → 59

Compound 59

[0103]

55 59 α MW : C₅₃H₅₇O₁₄F = 937.23
MP : 146 - 150°C
FAB(+)MS : m/z = 937 (M+H)⁺, 919 (M-OH)⁺

IR_v^{KBr} cm⁻¹ : 3414(O-H), 2948(C-H)
 1732, 1660, 1613(C=O)
 1267(C-C(=O)-O)
 1106(O-C-C)

5

¹H-NMR (ppm, 500 MHz, CDCl₃, Ref = 0.000ppm(TMS))

1 5.465 (1H, d, J_{1,2} = 4.03Hz)
 2 5.287 (1H, dd, J_{2,1} = 4.03, J_{2,3} = 9.89)
 10 3 6.245 (1H, t, J_{3,2} = J_{3,4} = 9.89)
 4 5.370 (1H, t, J_{4,3} = J_{4,5} = 9.89)
 5 5.465 (1H, d, J_{5,4} = 9.89)
 -COOCH₃ 3.623 (3H, s)
 -C₆H₄CH₃ 2.373, 2.355, 2.306 (3H, s) x 3
 15 -C₆H₄CH₃ 7.862, 7.850, 7.784, 7.178, 7.165, 7.099 (2H, d, J = 8.06) x 6

598 MW : C₅₃H₅₇O₁₄F = 937.23

MP : 155 - 160°C

FAB(+)MS : m/z = 937 (M+H)⁺, 919 (M-OH)⁺

20

IR_v^{KBr} cm⁻¹ : 3440(O-H), 2950(C-H)
 1733, 1667, 1613(C=O)
 1280, 1265(C-C(=O)-O)
 1097(O-C-C)

25

¹H-NMR (ppm, 500 MHz, CDCl₃, Ref = 0.000ppm(TMS))

1 5.147 (1H, d, J_{1,2} = 7.70Hz)
 2 5.533 (1H, dd, J_{2,1} = 7.70, J_{2,3} = 9.16)
 30 3 5.911 (1H, t, J_{3,2} = 9.16, J_{3,4} = 9.52)
 4 5.598 (1H, t, J_{4,3} = J_{4,5} = 9.52)
 5 4.317 (1H, d, J_{5,4} = 9.52)
 -COOCH₃ 3.644 (3H, s)
 -C₆H₄CH₃ 2.373, 2.359, 2.308 (3H, s) x 3
 35 -C₆H₄CH₃ 7.857, 7.811, 7.768, 7.187, 7.171, 7.106 (2H, d, J = 8.06) x 6

Example 8

40 Synthesis of β -galacturonyldexamethasone and the toluoyl-protected derivative of β -galacturonyldexamethasone (Fig. 8)

1. Synthesis of β -galacturonyldexamethasone

[0104] 1) D-Galacturonic acid **61** (1.98 g) was dissolved in dehydrated methanol (100 ml), and to this solution was added a solution of diazomethane in ether in small portions under stirring until bubbling ceased. After the solvent was distilled off *in vacuo*, pyridine (4 ml) and acetic anhydride (8 ml) were added to the residue thus obtained under ice-cooling, and, while the reaction temperature was slowly raised to room temperature, the resulting mixture was stirred for 24 h. Then, after the addition of methanol under ice-cooling, the solvent was distilled off *in vacuo*. The residue was dissolved in chloroform, washed with copper sulfate solution, and then the chloroform layer was evaporated *in vacuo*. After 50 the residue was dissolved in chloroform (4 ml), a hydrogenbromide-acetic acid solution (10.0 ml) was added under ice-cooling, and the resulting mixture was stirred for 3.5 h. Then, to this mixture was added hydrogenbromide-acetic acid solution (2.0 ml) under ice-cooling, and the resulting mixture was stirred for 1 h. After the reaction solution was evaporated *in vacuo*, the residue was dissolved in chloroform (80 ml), washed with saturated sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off *in vacuo*, and the residue thus obtained was 55 purified by silica gel column chromaography (toluene:ethyl acetate = 4:1) to give **63** as white powder [1.17 g (yield 28.8%)].

61 \rightarrow **63**

Compound 63

[0105]

5 MW : C₁₃H₁₇O₉Br = 397.17
 MP : 131 - 134°C
 FAB(+)MS : m/z = 395, 397 (M+H)⁺

10 IR ν ^{KBr} cm⁻¹ : 1769, 1748(C=O), 1375(CH₃)
 1232, 1218(C-C(=O)-O)

15 ¹H-NMR (ppm, 500 MHz, CDCl₃, Ref = 0.000ppm(TMS))

1 6.772 (1H, d, J_{1,2} = 4.03Hz)
 2 5.108 (1H, dd, J_{2,1} = 4.03, J_{2,3} = 10.62)
 3 5.456 (1H, dd, J_{3,2} = 10.62, J_{3,4} = 3.30)
 4 5.833 (1H, dd, J_{4,3} = 3.30, J_{4,5} = 1.1)
 5 4.879 (1H, d, J_{5,4} = 1.1)
 -COOCH₃ 3.777 (3H, s)
 -COCH₃ 2.111 (3H, s)
 -COCH₃ 2.024 (6H, s)

20 [0106] 2) Dexamethasone 6 (0.82 g) was dissolved in chloroform (100 ml), and to this solution were added, under an argon atmosphere, molecular sieve 4A (1.57 g), silver carbonate (1.62 g) and 63 (1.02 g). The resulting mixture was stirred at room temperature for 2 days. After the reaction solution was filtered, the filtrate was washed with saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* gave crude 64' (1.86 g). Purification of crude 64' (0.16 g) by silica gel PLC plate (chloroform/methanol = 20/1) gave 64' [0.041 g (yield 26.0%)] as white powder.

25 30 63 + 6 → 64'

Compound 64'

[0107]

35 MW : C₃₅H₄₅O₁₄F = 708.73
 MP : 141 - 142°C
 FAB(+)MS : m/z = 709 (M+H)⁺

40 IR ν ^{KBr} cm⁻¹ : 3454(O-H)
 2950(C-H)
 1757, 1665(C=O)
 1237(C-C(=O)-O)

45 ¹H-NMR (ppm, 500 MHz, CDCl₃, Ref = 0.000ppm(TMS))

1 5.791 (1H, d, J_{1,2} = 4.40Hz)
 2 4.273 (1H, dd, J_{2,1} = 4.40, J_{2,3} = 5.86)
 3 5.260 (1H, dd, J_{3,2} = 5.86, J_{3,4} = 2.93)
 4 5.791 (1H, dd, J_{4,3} = 2.93, J_{4,5} = 4.39)
 5 4.867 (1H, d, J_{5,4} = 4.39)
 -COOCH₃ 3.753 (3H, s)
 -COCH₃ 2.091, 2.074 (3H, s)
 -CH₃ (ortho ester) 1.660 (3H, s)

55 [0108] 3) 64' (277.4 mg) was dissolved in a mixture of acetonitrile/water [100 ml(4/96, containing 0.1% TFA)], and this solution was applied in 20 ml-portions to HPLC column (μ -Bondasphere C₁₈-100 Å, flow rate 23.0 ml/min, detection wave length 254 nm (UV), eluent A/B = water/95% acetonitrile (both containing 0.1% TFA) = 94/6 → 80/20 →

38/62, eluted with the gradient for 30 min). Fractions containing product were evaporated *in vacuo*, and then lyophilized to give **64β** as white powder [67.5 mg (yield 24.3%)].

64' → 64β

5

Compound 64β

[0109]

10 MW : C₃₅H₄₅O₁₄F = 708.73

MP : 155 - 158°C

FAB(+)MS : m/z = 709 (M+H)⁺, 731 (M+Na)⁺

15 IR ν ^{KBr} cm⁻¹ : 3406(O-H), 1754, 1665(C=O)
1225(C-C(=O)-O)

¹H-NMR (ppm, 500 MHz, CDCl₃, Ref = 0.000ppm(TMS))

20 1 4.893 (1H, d, J_{1,2} = 8.06Hz)
2 5.277 (1H, dd, J_{2,1} = 8.06, J_{2,3} = 10.26)
3 5.100 (1H, dd, J_{3,2} = 10.26, J_{3,4} = 3.29)
4 5.689 (1H, dd, J_{4,3} = 3.29, J_{4,5} = 1.46)
5 4.297 (1H, d, J_{5,4} = 1.46)
-COOCH₃ 3.764 (3H, s)
25 -COCH₃ 2.144, 2.096, 2.001 (3H, s) x 3

[0110] 4) **64'** (103.3 mg) was dissolved in methanol (5 ml), and to this solution was added 1 M sodium methoxide (0.5 ml) at 0°C. The resulting solution was stirred at room temperature for 3 h. After the reaction solution was evaporated *in vacuo*, 1 M sodium methoxide (0.5 ml) and water (1 ml) were added to the residue at 0°C, and stirred at room temperature for 2 h. The reaction solution was evaporated *in vacuo*, and then lyophilized, was purified by HPLC under similar conditions as in 3). Fractions containing the product were evaporated *in vacuo* and then lyophilized to give **65β** [29.5 mg (yield 35.5%)] and **66** [31.3 mg (yield 39.0%)], both as white powder.

64' → 65β + 66

35

Compound 65β

[0111]

40 MW : C₂₈H₃₇O₁₁F = 568.59

MP : 187 - 189°C

FAB(+)MS : m/z = 569 (M+H)⁺, 591 (M+Na)⁺

45 IR ν ^{KBr} cm⁻¹ : 3414(O-H), 1713, 1662(C=O)
1617, 1605(C-C)

¹H-NMR (ppm, 500 MHz, CD₃OD, Ref = 3.300ppm(CH₃OD))

50 1 4.134 (1H, d, J_{1,2} = 7.70Hz)
2 3.617 (1H, dd, J_{2,1} = 7.70, J_{2,3} = 9.89)
3 3.558 (1H, dd, J_{3,2} = 9.89, J_{3,4} = 3.30)
4 4.157 (1H, dd, J_{4,3} = 3.30, J_{4,5} = 1.10)
5 4.217 (1H, d, J_{5,4} = 1.10)

55

Compound 66

[0112]

5 MW : C₂₈H₃₅O₁₀F = 550.58
 MP : 183 - 184°C
 FAB(+)MS : m/z = 551 (M+H)⁺, 573 (M+Na)⁺

10 IR ν ^{KBr} cm⁻¹: 3414(O-H), 1713, 1662(C=O)
 1617, 1605(C-C), 1242(C-C(=O)-O)

¹H-NMR (ppm, 500 MHz, CD₃OD, Ref = 3.300ppm(CH₃OD))

15 1 6.151 (1H, d, J_{1,2} = 4.03Hz)
 2 4.012 (1H, t, J_{2,1} = J_{2,3} = 4.03)
 3 3.868 (1H, t, J_{3,2} = J_{3,4} = 4.03)
 4 5.098 (1H, d, J_{4,3} = 4.40)

2. Synthesis of toluoyl-protected derivative of β -galacturonyldexamethasone

20 [0113] 1) D-Galacturonic acid 61 (1.12 g) was dissolved in dehydrated methanol (30 ml), and to this solution was added, under stirring, diazomethane in ether in small portions until bubbling ceased. After removal of the solvent *in vacuo*, pyridine (5 ml), *p*-toluoyl chloride (5 ml) and chloroform (10 ml) were added to the residue under ice-cooling, and the resulting mixture was stirred for 4 h, while the reaction temperature was slowly raised to room temperature. Then, 25 to the reaction mixture was added water under ice-cooling, and the chloroform layer was washed successively with water, saturated solutions of sodium bicarbonate and copper sulfate. After the solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. Purification of the residue thus obtained by silica gel column chromatography (toluene:ethyl acetate = 40/1 → 30/1) gave 67 as white powder [782.7 mg (yield 20.2%)].

30 61 → 67Compound 67B

[0114]

35 MW : C₃₉H₃₆O₁₁ = 680.706
 MP : 180 - 182°C
 FAB(-)MS : m/z = 679 (M-H)⁺

40 IR ν ^{KBr} cm⁻¹: 1771, 1733, 1613(C = O)
 1267(C-C(=O)-O)
 1093(O-C-C)

¹H-NMR(ppm, 500MHz, CDCl₃, Ref = 0.000ppm(TMS))

45 1 6.215 (1H, d, J_{1,2} = 8.06Hz)
 2 6.065 (1H, dd, J_{2,1} = 8.06, J_{2,3} = 10.26)
 3 5.733 (1H, dd, J_{3,2} = 10.26, J_{3,4} = 3.30)
 4 6.207 (1H)
 5 4.809 (1H, d, J_{5,4} = 1.47)
 -COOCH₃ 3.700 (3H, s)
 -C₆H₄CH₃ 2.434, 2.378, 2.310, 2.296 (3H, s) x 4
 -C₆H₄CH₃ 7.953, 7.951, 7.769, 7.710, 7.266, 7.205, 7.101, 7.072 (2H, d, J = 8.06) x 8

55 [0115] 2) 67 (70.3 mg) was dissolved in dichloromethane (5 ml), and to this solution was added, under ice-cooling, a hydrogenbromide-acetic acid solution (2 ml). The mixture was stirred at room temperature for 2 h. The reaction solution was washed with saturated sodium bicarbonate solution, and then dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* gave 68 [44.6 mg (yield 69.2%)] as white powder.

67 → 68Compound 68

5 [0116]

MW : C₃₁H₂₉O₉Br = 625.468
 FAB(+)MS : m/z = 625, 627 (M+H)⁺
¹H-NMR(ppm, 500MHz, CDCl₃, Ref = 0.000ppm(TMS))

10 1 7.003 (1H, d, J_{1,2} = 4.03Hz)
 2 5.612 (1H, dd, J_{2,1} = 4.03, J_{2,3} = 10.26)
 3 6.006 (1H, dd, J_{3,2} = 10.26, J_{3,4} = 3.30)
 4 6.255 (1H, dd, J_{4,3} = 3.30, J_{4,5} = 1.46)
 15 5 5.132 (1H, d, J_{5,4} = 1.46)
 -COOCH₃ 3.724 (3H, s)
 -C₆H₄CH₃ 2.429, 2.359, 2.316 (3H, s) x 3
 -C₆H₄CH₃ 7.895, 7.866, 7.695, 7.710, 7.254, 7.183, 7.073 (2H, d, J = 8.06) x 6

20 [0117] 3) Dexamethasone 6 (88.0 mg) was dissolved in dehydrated tetrahydrofuran (10 ml), and to this solution were added, under an argon atmosphere, molecular sieve 5A (1.0 g) and 68 (100.8 mg) dissolved in dehydrated tetrahydrofuran (10 ml). Then, to the resulting mixture were added, under ice-cooling, silver triflate (82.2 mg) dissolved in dehydrated tetrahydrofuran (2 ml) and tetramethylurea (0.25 ml), and, while the reaction temperature was slowly raised to room temperature, the resulting mixture was stirred for 2 h. The reaction solution was filtered, and the solvent of the 25 filtrate was evaporated *in vacuo*. The residue thus obtained was dissolved in ethyl acetate (100 ml), washed with saturated sodium chloride solution. The solvent of the solution was evaporated *in vacuo*. The residue thus obtained was purified by HPLC (column: μ -Bondasphere C₁₈-100 Å, flow rate 23.0 ml/min, detection wave length 254 nm (UV), eluent A/B = water/95% acetonitrile (both containing 0.1% TFA) = 30/70 → 0/100, eluted with gradient for 30 min). Fractions containing product were evaporated *in vacuo*, and lyophilized to give 69 α [9.5 mg (yield 4.6%)] and 69 β [38.1 mg (yield 30 18.5%)], both as white powder.

68 + 6 → 69Compound 6935 69 α

[0118]

40 MW : C₅₃H₅₇O₁₄F = 937.023
 MP : 161 - 167°C
 FAB(+)MS : m/z = 937 (M+H)⁺, 919 (M-OH)⁺

45 IR ν^{KBr} cm⁻¹: 3414(O-H), 2928(C-H)
 1731, 1667, 1612(C = O)
 1283, 1267(C-C(=O)-O)
 1095(O-C-C)

50 ¹H-NMR(ppm, 500MHz, CDCl₃, Ref = 0.000ppm(TMS))
 1 5.542 (1H, d, J_{1,2} = 4.03Hz)
 2 5.634 (1H, dd, J_{2,1} = 4.03, J_{2,3} = 10.63)
 3 6.065 (1H, dd, J_{3,2} = 10.63, J_{3,4} = 3.30)
 4 6.251 (1H, dd, J_{4,3} = 3.30, J_{4,5} = 1.46)
 55 5 5.231 (1H, d, J_{5,4} = 1.46)
 -COOCH₃ 3.678 (3H, s)
 -C₆H₄CH₃ 2.424, 2.347, 2.310 (3H, s) x 3
 -C₆H₄CH₃ 7.894, 7.858, 7.696, 7.244, 7.156, 7.061 (2H, d, J = 8.06) x 6

69B

[0119]

5 MW : C₅₃H₅₇O₁₄F = 937.023
 MP : 161 - 165°C
 FAB(+)MS : 937 (M+H)⁺, 919 (M-OH)⁺

10 IR v^{KBr} cm⁻¹ : 3412(O-H), 2930(C-H)
 1733, 1666, 1612(C = O)
 1283, 1266(C-C(=O)-O),
 1095(O-C-C)

15 ¹H-NMR(ppm, 500MHz, CDCl₃, Ref = 0.000ppm(TMS))

1	5.151 (1H, d, J _{1,2} = 8.42Hz)
2	5.904 (1H, dd, J _{2,1} = 8.42, J _{2,3} = 10.26)
3	5.632 (1H, dd, J _{3,2} = 10.26, J _{3,4} = 3.30)
4	6.029 (1H, dd, J _{4,3} = 3.30, J _{4,5} = 1.10)
20 5	5.565 (1H, d, J _{5,4} = 1.10)
-COOCH ₃	3.760 (3H, s)
-C ₆ H ₄ CH ₃	2.373, 2.361, 2.299 (3H, s) x 4
-C ₆ H ₄ CH ₃	7.975, 7.852, 7.706, 7.285, 7.178, 7.071 (3H, d, J = 8.06) x 6

25 Example 9Synthesis of β -fucosylexamethasone (Fig. 9)1) Synthesis of SMe derivative of fucose (71 \rightarrow 72 \rightarrow 73 α + 73 β)

30 [0120] L-(-)Fucose 71 [3.0 g (18.27 mmol)] was suspended in acetic anhydride (30 ml), and to this solution was added, at 0°C, pyridine (7.1 ml) drop-wise. The mixture was stirred at room temperature overnight. The reaction solution was poured into ice-water, and extracted with chloroform four times. After the chloroform layer was washed successively with copper sulfate solution, water three times, and saturated sodium chloride solution. After the organic layer was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. The residue thus obtained was dissolved in ethyl acetate, and allowed to stand at -30°C for 2 days. Precipitated crystals were collected by filtration, weighing 2.98 g (yield 51.6%) of 72 as white powder. The product thus obtained [2.0 g (6.32 mmol)] and Bu₃SnSMe [3.20 g (9.48 mmol)] were dissolved in dichloroethane (20 ml), and to this solution was added at 0°C tin(IV) chloride [0.96 ml (8.22 mmol)] drop-wise. The mixture was stirred at room temperature overnight. The reaction solution was diluted with chloroform, and to this mixture was added potassium fluoride. After stirring, the mixture was filtered through celite. The chloroform layer of the filtrate was washed with saturated sodium bicarbonate, water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and the solvent was distilled off *in vacuo*. Purification of the residue thus obtained by silica gel column chromatography (ethyl acetate:toluene = 1:6) gave α -anomer (73 α) [164.2 mg (yield 8.1%)] and β -anomer (73 β) [1.483 g (yield 73.2%)], both as white powder.

45 Compound 73 α

[0121]

50 C₁₃H₂₀O₇S
 MW : 320.36
 MP : 78 - 80°C
 FAB(+)MS : 321 (M+H)⁺, 641 (2M+H)⁺
 IR v^{KBr} cm⁻¹ : 1755, 1742(OCOCH₃)
 55 ¹H-NMR [500MHz, CDCl₃, Ref = 0.000ppm(TMS)]

δ: 1.169 (3H, d, J = 6.6Hz, H-6)
 1.991, 2.053, 2.071, 2.170 (each 3H, 4s, SCH₃+3Ac)

4.449 (1H, q, J = 6.6Hz, H-5)
 5.239 (1H, dd, J = 3.3, 10.6Hz, H-3)
 5.291 (1H, dd, J = 5.5, 10.6Hz, H-2)
 5.299 (1H, dd, J = 0.7, 3.3Hz, H-4)
 5.568 (1H, d, J = 5.5Hz, H-1)

5

Compound 73β

[0122]

10

$C_{13}H_{20}O_7S$
 MW : 320.36
 MP : 146 - 147°C
 FAB(+)MS : 321 (M+H)⁺, 641 (2M+H)⁺
 15 $IR_{v}^{KBr} cm^{-1}$: 1746(OCOCH₃)
¹H-NMR [500MHz, CDCl₃, Ref = 0.000ppm(TMS)]

20

δ : 1.224 (3H, d, J = 6.2Hz, CH₃-6)
 1.990, 2.074, 2.178, 2.200 (each 3H, 4s, SCH₃+3Ac)
 3.850 (1H, dq, J = 1.1, 6.2Hz, H-5)
 4.361 (1H, d, J = 9.9Hz, H-1)
 5.057 (1H, dd, J = 3.3, 9.9Hz, H-3)
 5.248 (1H, t, J = 9.9Hz, H-2)
 5.282 (1H, dd, J = 1.1, 3.3Hz, H-4)

25

2) Synthesis of a protected derivative of fucosyldexamethasone

30

[0123] To a mixture of dexamethasone (6) [51 mg (0.130 mmol)], β -anomer (73β) of fucose SMe-derivative [50 mg (0.156 mmol)] and molecular sieve 4A (100 mg) was added tetrahydrofuran (about 1 ml), and then, under an argon atmosphere at -20°C, methyl triflate (36 μ l) was added. After stirring at room temperature for 2.5 h, the reaction mixture was neutralized with Et₃N, diluted with ethyl acetate, and filtered. The filtrate was washed successively with saturated solutions of sodium bicarbonate and sodium chloride. After the solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. Purification of the residue thus obtained by silica gel column chromatography (ethyl acetate:toluene = 1:1) gave α -anomer (74α) [6.5 mg (yield 7.5%)] and β -anomer (74β) [20.9 mg (yield 24.2%)], both as white powder.

35

Compound 74α (fuc(OAc)dexa(α))

40

[0124]

$C_{34}H_{45}FO_{12}$ MW = 664.72
 MP : 120 - 121°C
 45 FAB(+)MS 665 (M+H)⁺
 $IR_{v}^{KBr} cm^{-1}$ 3470(O-H)
 1750(C=O of OAc)
 1662(C=O at position-3)
 50 1622, 1604(C = C)
 1070, 1058(C-O of OH)

55

¹H-NMR(500MHz, CDCl₃, Ref = 0.000ppm(TMS))
 δ : 0.896 (3H, d, J = 6.6Hz, 16-CH₃)
 1.028 (3H, s, CH₃)
 1.150 (3H, d, J = 6.6 Hz, H₃-6_{fuc})
 1.543 (3H, s, CH₃)

2.000 (3H, s, Ac)
 2.171 (6H, s, 2Ac)
 4.253 (1H, q, J = 6.6Hz, H-5_{fuc})
 4.386 (1H, d, J = 17.2Hz, H-21)
 5 4.516 (1H, d, J = 17.2Hz, H'-21)
 5.028 (1H, d, J = 3.7 Hz, H-1_{fuc})
 5.171 (1H, dd, J = 3.7, 11.0Hz, H-2_{fuc})
 5.310 (1H, dd, J = 1.1, 3.3 Hz, H-4_{fuc})
 5.436 (1H, dd, J = 3.3, 11.0Hz, H-3_{fuc})
 10 6.112 (1H, s, H-4)
 6.331 (1H, dd, J = 1.8, 10.3Hz, H-1)
 7.189 (1H, dd, J = 10.3Hz, H-2)

Compound 74 β (fuc(OAc)dexa(β))
 15 [0125]

$C_{34}H_{45}FO_{12}$ MW = 664.72
 MP : 134 - 137°C
 20 FAB(+)MS 665 (M+H)⁺

IR_v^{KBr} cm⁻¹ 3494(O-H)
 1754(OOCOCH₃)
 1666(C = O)
 25 1623, 1604(C = C)
 1075, 1035(C-O)

¹H-NMR(500MHz, CDCl₃, Ref = 0.000 ppm(TMS))

30 δ : 0.905 (3H, d, J = 7.3Hz, 16-CH₃)
 0.993 (3H, s, CH₃)
 1.220 [3H, d, J = 6.6Hz, H₃-6(fuc)]
 1.549 (3H, s, CH₃)
 1.998, 2.113, 2.167 (each 3H, 3s, 3OAc)
 35 3.806 [1H, d, J = 0.7, 6.6Hz, H-5(fuc)]
 4.484 (1H, d, J = 16.5Hz, H-21)
 4.562 (1H, d, J = 16.5Hz, H-21)
 5.564 [1H, d, J = 7.7Hz, H-1(fuc)]
 5.040 [1H, dd, J = 3.3, 10.6Hz, H-3(fuc)]
 40 5.227 [1H, dd, J = 7.7, 10.6Hz, H-2(fuc)]
 5.240 [1H, dd, J = 3.3, 0.7Hz, H-4(fuc)]
 6.110 (1H, s, H-4)
 6.325 (1H, dd, J = 2.2, 9.9Hz, H-1)
 7.237 (1H, d, J = 9.9Hz, H-2)

45 3) Synthesis of deprotected derivative of fucosylexamethasone (74 β \rightarrow 75 β)

[0126] A protected derivative of fucosylexamethasone (74 β) [112.4 mg (0.169 mmol)] was dissolved in methanol (1 ml), and to this solution was added 1 M sodium methoxide (35 μ l). The mixture was stirred at room temperature for 50 1 h. The reaction solution was applied to a gel filtration column of LH-20, and eluted with methanol. Evaporation of the solvent of fractions containing the product *in vacuo* gave 75 β [79.4 mg (yield 87.2%)] as white powder.

Compound 75 β

55 [0127]

$C_{28}H_{39}FO_9$ MW = 538.61
 MP : 161 - 164°C

FAB(+)MS 539 (M+H)⁺

IR_v^{KBr} cm⁻¹ 3418 (OH)
 1717, 1665 (C=O), 1622, 1602 (C=C)

5 ¹H-NMR (500MHz, CD₃OD, Ref = 3.350 ppm (CH₃OD)

δ : 0.906 (3H, d, J=7.3Hz, 16-CH₃)
 1.054 (3H, s, CH₃)
 10 1.318 (3H, d, J=6.6Hz, H₃-6_{fuc})
 1.628 (3H, s, CH₃)
 3.516 (1H, dd, J=3.3, 9.9Hz, H-3_{fuc})
 3.604 (1H, dd, J=7.3, 9.9Hz, H-2_{fuc})
 3.631 (1H, d, J=3.3Hz, H-4_{fuc})
 15 3.682 (1H, q, J=6.6Hz, H-5_{fuc})
 4.239 (1H, d, J=7.3Hz, H-1_{fuc})
 4.683 (2H, s, H₂-21)
 6.120 (1H, s, H-4)
 6.329 (1H, dd, J=1.8, 10.3Hz, H-1)
 20 7.445 (1H, d, J=10.3Hz, H-2)

Example 10

Synthesis of sodium salt of sialyldexamethasone (Fig. 10)

25 1) Synthesis of a protected derivative of sialyl dexamethasone

[0128] Methyl 2-chloro-4,7,8,9-tetra-O-acetyl-N-acetyleneuraminate (81) was synthesized by the method described in Carbohy. Res. 158 (1986), 35-51.

30 [0129] Dexamethasone (6) [7.0 g (18.0 mmol)] was dissolved in tetrahydrofuran (130 ml), and to this solution were added molecular sieve 4A (70 g) and methyl 2-chloro-4,7,8,9-tetra-O-acetyl-N-acetyleneuraminate (81) [11.08 g (21.6 mmol)]. To this mixture was added, under an argon atmosphere, a solution of silver triflate [5.60 g (21.6 mmol)] in tetrahydrofuran at -40°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 1.5 h. To this mixture was further added 81 [4.63 g (9.0 mmol)], and the resulting mixture was stirred at room temperature overnight. After the reaction solution was filtered, the solvent of the filtrate was evaporated *in vacuo*. The residue was dissolved in ethyl acetate (200 ml), washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After the solvent was distilled off *in vacuo*, the residue thus obtained was purified by silica gel column chromatography (chloroform:methanol = 20:1) to give (84α) [9.26 g (yield 59.4%)] as white powder, yellow powder (3.99 g) and the starting material (6) recovered [1.72 g (24.6% recovery)]. Recrystallization of 84α from ethyl acetate gave 84α as white crystals (5.89 g). Purification of yellow powder (3.9 g) by HPLC (silica gel cartridge column, eluent chloroform: methanol = 100:1 → 50:1) gave 84β as white powder [1.80 g (yield 11.6%)].

Compound 84α (crystals)

45 [0130]

C₄₂H₅₆FNO₁₇
 MW = 865.90
 MP = 156°C
 50 FAB(+)MS 866 (M+H)⁺

IR_v^{KBr} cm⁻¹ : 3520 (OH,NH)
 1749, 1666 (C=O)
 1624 (C=C)
 55 1540 (NH)
 1039 (C-O)

¹H-NMR [500MHz, CDCl₃, Ref=0.000 ppm (TMS)]

δ : 0.926 (3H, d, J=7.3Hz, 16-CH₃)
 1.015 (3H, s, CH₃)
 1.537 (3H, s, CH₃)
 1.877, 2.029, 2.044, 2.148, 2.159 (each 3H, 5s, 5Ac)
 5 2.794 (1H, dd, J=4.8, 12.8Hz, H-3_{eq}NeuNAc)
 3.748 (1H, dd, J=2.2, 10.6Hz, H-6_{NeuNAc})
 3.788 (1H, s, COOCH₃)
 4.022 (1H, dd, J = 5.9, 12.5 Hz, H-9_{NeuNAc})
 4.029 (1H, t, J = 10.6Hz, H-5_{NeuNAc})
 10 4.261 (1H, dd, J = 2.6, 12.5 Hz, H-9_{NeuNAc})
 4.278 (1H, d, J = 18.7Hz, H-21)
 4.920 (1H, ddd, J = 4.8, 10.6, 12.1Hz, H-4_{NeuNAc})
 5.105 (1H, d, J = 18.7Hz, H-21)
 5.121 (1H, d, J = 9.9Hz, NH)
 15 5.285 (1H, dd, J = 2.2, 9.5Hz, H-7_{NeuNAc})
 5.474 (1H, ddd, J = 2.6, 5.9, 9.5Hz, H-8_{NeuNAc})
 6.106 (1H, s, H-4)
 6.324 (1H, dd, J = 1.8, 10.3 Hz, H-1)
 7.212 (1H, d, J = 10.3Hz, H-2)

20 81+6 → 84g+84h

Compound 84g (crystals)

25 [0131]

$C_{42}H_{56}FNO_{17}$
 MW = 865.90
 MP = 194 - 197°C
 30 FAB (+) MS 866 (M+H)⁺, 888 (M+Na)⁺
¹H-NMR [500 MHz, CDCl₃, Ref = 0.000ppm(TMS)]

 δ : 0.857 (3H, d, J = 7.3 Hz, 16-CH₃)
 1.031 (3H, s, CH₃)
 35 1.547 (3H, s, CH₃)
 1.896, 1.995, 2.027, 2.044, 2.153 (each 3H, 5s, 5Ac)
 2.553 (1H, dd, J = 5.1, 12.8 Hz, H-3_{eq}NeuNAc)
 3.885 (1H, dd, J = 10.3, 12.8Hz, H-9_{NeuNAc})
 4.093 (1H, q, J = 10.3Hz, H-5_{NeuNAc})
 40 4.378 (1H, dd, J = 2.2, 10.3 Hz, H-5_{NeuNAc})
 4.498 (1H, d, J = 17.6Hz, H-21)
 4.796 (1H, d, J = 17.6Hz, H-21)
 5.114 - 5.156 (2H, m, H-8_{NeuNAc} + H-9_{NeuNAc})
 5.379 (1H, t, J = 2.2Hz, H-7_{NeuNAc})
 45 5.399 (1H, dt, J = 5.1, 10.3Hz, H-4_{NeuNAc})
 5.520 (1H, d, J = 10.3Hz, NH)
 6.113 (1H, s, H-4)
 6.331 (1H, dd, J = 1.8, 10.3 Hz, H-1)
 7.211 (1H, d, J = 10.3Hz, H-2)
 50 IR ν^{KBr} cm⁻¹ : 3572, 3494 (OH,NH)
 1767, 1755, 1735, 1663(C=O)
 1625, 1605 (C=C)

2) Synthesis of a deprotected derivative of sialyldexamethasone (α)

55 [0132] 84g [2.98 g (3.45 mmol)] was dissolved in methanol (20 ml), and to this solution was added 1 M sodium methoxide (0.7 ml) at 0°C. The mixture was stirred at room temperature for 2 h. The solvent was distilled off from the reaction mixture *in vacuo*, and to the residual material were added water (10 ml) and 1 M sodium methoxide (3.4 ml).

The mixture was stirred at room temperature for 30 min. Then the reaction solution was applied to a gel filtration column of LH-20, and eluted with methanol. The solvent was distilled off from fractions containing product *in vacuo* to give **85 α** as white powder [2.30 g (94.7%)]. **85 α** was further recrystallized from methanol to give colorless crystals (1.20 g).

5 Compound **85 α** (crystals)

[0133]

10 C₃₃H₄₅FNO₁₃Na
MW = 705.71
MP = 214°C (decomp.)
FAB (+)MS 706 (M+H)⁺, 728 (M+Na)⁺

15 IR ν ^{KBr} cm⁻¹ : 3374 (OH,NH)
 1727, 1664 (C=O)
 1615 (COONa)
 1559 (NH)
 1069, 1041 (C-O)

20 ¹H-NMR [500 MHz, CD₃OD, Ref = 0.000ppm(TMS)]

25 δ : 0.839 (3H, d, J = 7.3 Hz, 16-CH₃)
 1.008 (3H, s, CH₃)
 1.583 (3H, s, CH₃)
 1.705 (1H, t, J = 12.1Hz, H-3_{ax} NeuNAc)
 2.010 (3H, s, Ac)
 2.880 (1H, dd, J = 4.4, 12.1 Hz, H-3_{eq} NeuNAc)
 3.442 (1H, dd, J = 2.2, 9.2Hz, H-7_{NeuNAc})
 3.597 (1H, dd, J = 6.6, 11.4 Hz, H-9_{NeuNAc})
 3.836 (1H, dd, J = 2.2, 11.4 Hz, H-9_{NeuNAc})
 3.905 (1H, ddd, J = 2.2, 6.6, 9.2Hz, H-8_{NeuNAc})
 4.595 (1H, d, J = 18.7Hz, H-21)
 4.683 (1H, d, J = 18.7Hz, H'-21)
 6.068 (1H, s, H-4_{NeuNAc})
 6.281 (1H, dd, J = 1.8, 10.3 Hz, H-1)
 7.408 (1H, d, J = 10.3Hz, H-2)

84 α →85 α

40 3) Synthesis of a deprotected derivative of sialylxexamethasone (β)

[0134] **84 β** [506.1 mg (0.584 mmol)] was dissolved in methanol (50 ml), and to this solution was added 1 M sodium methoxide (0.7 ml). The mixture was stirred at room temperature for 2 h. The solvent was distilled off from the reaction solution *in vacuo*, and to the residue were added water (3 ml), 1 M sodium methoxide (0.58 ml) and methanol (1 ml).
45 The resulting mixture was stirred at room temperature for 1 h. Then the reaction solution was applied to a gel filtration column of LH-20, and eluted with methanol. The solvent was distilled off from fractions containing product *in vacuo* to give **85 β** as white powder [389.3 mg (yield 94.5%)].

Compound **85 β**

[0135]

50 C₃₃H₄₅FNO₁₃Na
MW = 705.71
MP = 228 - 229 °C (decomp.)
FAB (+) MS 706 (M+H)⁺, 728 (M+Na)⁺
¹H-NMR [500 MHz, CD₃OD, Ref = 0.000ppm(TMS)]

δ :	0.826 (3H, d, J = 7.3 Hz, 16-CH ₃) 1.001 (3H, s, CH ₃) 1.587 (3H, s, CH ₃) 1.979 (3H, s, Ac)
5	2.448 (1H, dd, J = 5.1, 12.8 Hz, H-3 _{eq} NeuNAc) 3.408 (1H, d, J = 10.3Hz, H-6 _{NeuNAc}) 3.643 (1H, dd, J = 5.1, 11.4 Hz, H-9 _{NeuNAc}) 3.714 (1H, d, J = 10.3Hz H-7 _{NeuNAc}) 3.787 (1H, dd, J = 2.9, 11.4Hz, H-9 _{NeuNAc})
10	3.950 (1H, t, J = 10.3Hz, H-5 _{NeuNAc}) 4.109 (1H, dt, J = 5.1, 10.3Hz, H-4 _{NeuNAc}) 4.300 (1H, d, J = 18.3Hz, H-21) 4.611 (1H, d, J = 18.3Hz, H-21) 6.068 (1H, s, H-4)
15	6.289 (1H, dd, J = 1.8, 9.9Hz, H-1) 7.419 (1H, d, J = 9.9Hz, H-2)
IR ν ^{KBr} cm ⁻¹ :	3400 (OH, NH) 1721, 1663(C = O) 1623(COONa) 20 1560(NH) 1067, 1023(C- O)

84β → 85β25 Example 11

Synthesis of sialylbetamethasone (Fig. 11)

1) Sialylbetamethasone (glycosylation)

30 [0136] Betamethasone (86) (1.0 g) was dissolved in tetrahydrofuran (20 ml), and to this solution were added silver triflate (1.31 g) and molecular sieve 5A (1.0 g). To this mixture was added, under an argon atmosphere and at - 40°C, a solution of methyl 2-chloro-4,7,8,9-tetra-O-acetyl-N-acetylneuraminic acid (81) (2.08 g) in tetrahydrofuran. While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 5 h. The reaction solution was filtered, and the solvent was distilled off from the filtrate *in vacuo*. The residue was dissolved in chloroform, and the solution was washed with saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (chloroform:methanol = 15:1), and further purified by Lobar column using silica gel column (diisopropyl ether:methanol = 5:1) to give 87 as white powder [953.9 mg (yield 43.4%)].

40 81 + 86 → 87Compound 87

45 [0137]

C₄₂H₅₆FNO₁₇ MW = 865.90
¹H-NMR [500 MHz, CDCl₃, Ref 0.00ppm (TMS)]
 • NeuAc

50	3 eq	2.813 (1H, dd, J _{3,8x} + 3 _{eq} = 4.76, J _{3,eq} + 4 = 12.46)
	4	4.896 (1H, ddd, J _{4,5} = 10.26)
	5	4.058 (1H, t, J _{5,6} = 10.63)
	6	3.727 (1H, dd, J _{6,7} = 2.19)
55	7	5.302 (1H, dd, J _{7,8} = 9.90)
	8	5.483 (1H, ddd, J _{8,9} = 2.93)
	9	4.251 (1H, dd, J _{9,9'} = 12.45)
	9'	4.014 (1H, dd, J _{8,9'} = 6.22)

OAc x 5 2.151, 2.044, 2.025, 1.868 (15H, s)
COOCH₃ 3.822 (3H, s)

5 IR ν ^{KBr} cm⁻¹ 3500(O-H), 1748(C=O position-20), 1663(C=O position-3)
FAB (+) MS 866(M+H)⁺, 806(M-COOCH₃)⁺
MP : 145 - 148°C

2) Deprotection of a protected derivative of sialylbetamethasone

10 [0138] 87 (402 mg) was dissolved in methanol (4 ml), and to this solution was added 1 M sodium methoxide (0.45 ml) at 0 - 5°C. The mixture was stirred at room temperature for 3 h. After the solvent of the reaction solution was evaporated *in vacuo*, water (2 ml) and 1 M sodium methoxide (0.46 ml) were added to the residue, and the resulting mixture was stirred at room temperature for 30 min. The reaction solution was applied to a gel filtration column of LH-20, and eluted with methanol. The solvent was distilled off from fractions containing product *in vacuo* to give pale yellow powder (329.4 mg). A portion of the yellow powder (269 mg) was purified by HPLC using a reversed phase partition column (acetonitrile-water) to give 89 β [32.4 mg (yield 12.5%)] and 89 α [134 mg (yield 51.7%)], respectively, both as white powder.
15 [0139] Furthermore, a remaining portion of the product (60 mg) was treated with activated carbon to give 90 [38.0 mg (yield 63.7%)] as yellowish white powder.

20 Compounds 89 β , 89 α and 90

[0140]

25 Compounds 89 β and 89 α C₃₃H₄₆FNO₁₃ MW = 683.723
Compound 90 C₃₃H₄₆FNO₁₃Na MW = 705.704

Compound 89 β

30 [0141]

¹H-NMR [500 MHz, CD₃OD, Ref = 3.30ppm (CH₃OD)]

35 3_{ax} 1.689 (1H, dd, J_{3ax} + 4 = 11.36, J_{3ax} + 3_{eq} = 12.82)
3_{eq} 2.432 (1H, dd, J_{3eq} + 4 = 5.12)
4 4.164 (1H, ddd, J_{4,5} = 10.99)
5 3.832 (1H, t, J_{5,6} = 10.25)
6 3.602 (1H, dd, J_{6,7} = 11.36)
9 3.745 (1H, dd, J_{9,8} = 5.50, J_{9,9'} = 9.53)
40 9' 3.462 (1H, dd, J_{9,9'} = 9.53)
Ac 2.004 (3H, s)

FAB(-)MS 682(M-H)⁺

45 Compound 89 α

[0142]

¹H-NMR [500 MHz, DMSO, Ref = 2.50ppm(DMSO)]

50 3_{ax} 1.530 (1H, d, J_{3ax} + 3_{eq} = 12.46)
3_{eq} 2.561 (1H, dd, J_{3eq} + 4 = 4.40)

55 FAB(-)MS 682 (M-H)⁺
MP : 156 - 159°C

Compound 90

[0143]

5 FAB(-)MS 704 (M-H)⁺
¹H-NMR [500 MHz, CD₃OD, Ref = 3.30ppm (CH₃OD)]

10 1 : 6.066 (1H, s)
3ax : 1.711 (1H, t, J = 12.09)
3eq : 2.378 (1H, t, J = 4.03)

Example 12

Synthesis of glucosylbetamethasone (protected derivative: per-Tol) (Fig. 12)

15 $3 + 86 \rightarrow 91$ (glucosylation)

[0144] Betamethasone (86) (3.69 g) was dissolved in tetrahydrofuran (200 ml), and to this solution were added molecular sieve 5A (4.90 g) and silver triflate (4.83 g). To this mixture was added, under an argon atmosphere and at 0 - 5°C, a solution of a glucose bromide (protected derivative: per-Tol) (3) (13.45g) dissolved in tetrahydrofuran (70 ml). While the reaction temperature was raised slowly to room temperature, the mixture was stirred for 6 h. To this mixture was further added silver triflate (4.83 g), and the resulting mixture was stirred overnight. The reaction solution was filtered, and the solvent was distilled off from the filtrate *in vacuo*. The residue was dissolved in chloroform, and the chloroform solution was washed saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. The residue thus obtained was purified by silica gel chromatography (toluene:ethyl acetate = 3:1) to give white powder [2.87 g(yield 29.7%)]. This product was further purified by HPLC using a reversed phase partition column to give 91 β [1.46 g (yield 15.1%)] and 91 α [0.17 g (yield 1.8%)], respectively, both as white powder.

30 Compound 91 [glucosylbetamethasone (protected derivative: per Tol)]

[0145]

35 Molecular formula C₆₀H₆₃FO₁₄
MW 1027.148

Glucosylbetamethasone (per Tol) β -anomer (91 β)

[0146]

40 ¹H-NMR [500 MHz, CDCl₃, Ref = 0.000ppm(TMS)]

45 1: 5.012 (1H, d, J_{1,2} = 8.06)
2: 5.516 (1H, t, J_{2,3} = 9.89)
3: 5.872 (1H, t)
4: 5.642 (1H, t)
5: 4.097 (1H, t)
(CH₃C₆H₄CO-) x 4 : 7.865, 7.830, 7.782, 7.716 (each 2H, d)
(CH₃C₆H₄CO-) x 4 : 2.380, 2.347, 2.286 (12H, s)

50 IR ν ^{KBr} cm⁻¹ 3472(O-H), 1732(C = O position-20), 1665(C=O position-3)
FAB(+)MS 1027(M+H)⁺, 1009(M-OH)⁺
MP : 154 - 157°C

Glucosylbetamethasone (per Tol) α -anomer (91 α)

[0147]

5 $^1\text{H-NMR}$ [500 MHz, CDCl_3 , Ref = 0.000ppm(TMS)]

1: 5.254 (1H, d, $J_{1,2} = 4.03$)
 2: 5.205 (1H, dd, $J_{2,3} = 10.25$)
 3: 6.120 (1H, t)
 10 4: 5.741 (1H, t)
 6: 4.926 (1H, dd, $J_{6,6'} = 12.46$)
 6': 4.223 (1H, dd, $J_{5,6'} = 2.56$)
 $(\text{CH}_3\text{C}_6\text{H}_4\text{CO}-) \times 4$: 7.946, 7.872, 7.835, 7.764 (each 2H, d)
 $(\text{CH}_2\text{C}_6\text{H}_4\text{CO}-) \times 4$: 2.419, 2.366, 2.334, 2.294 (each 3H, s)

15 IR ν^{KBr} cm^{-1} 3478(O-H), 1731(C = O position-20), 1666(C=O position-3)
 FAB(+)MS 1027(M+H)⁺, 1009(M-OH)⁺
 MP : 159 - 162°C

20 (II) Evaluation of pharmacological activity

[0148] Ointment to be tested was prepared using white soft paraffin as the base and containing dexamethasone at 0.1% concentration.

25 1. Inhibitory effects on Granuloma growth (paper disk method)

1) Experimental method

[0149] Groups of 5 male Sprague-Dawley rats each weighing 150 - 170 g were used. Under ether anesthesia, the 30 dorsum of animals was closely clipped, and medianly incised. After each one pre-weighed paper disk (8-mm diameter, 1-mm thick, weighing about 30 mg; Toyo-Roshi filter paper) was inserted subcutaneously into both sides of the dorsal incision, the incision was sutured. In order to prevent bacterial infection, penicillin G potassium salt (2,000 units) per rat was intramuscularly injected after the surgery. Base or ointment to be tested (50 mg each) was rubbed carefully into the skin over the paper disk inserted site, for 30 seconds once a day for the duration of 7 days. Rats were slipped plastic cangs on to prevent them from licking the drug applied sites. On the 8th day of the test, rats were sacrificed under ether anesthesia, and granulomas were carefully excised. Granulomas were dried at 40°C for 24 h, and their dry weights were recorded.

35 2) Results

[0150] 40 Inhibitory effects of dexamethasone derivatives on the weight increase of granuloma of experimental animals as compared with those of control animals are shown as per cent of inhibition over the control in Table 1. Figures with asterisks in the table indicate significant difference. The same will be applied to the following other tables.

45

50

55

Table 1

Effects of dexamethasone derivatives on growth of granuloma

Test compound	Weight of granuloma	Test compound	Weight of granuloma
Control	0.0±5.8	45'	-11.8±10.1
White soft paraffin (base)	-0.6±6.1	54 β	-35.1± 2.8**
Betamethasone valerate	-22.5±5.7*	54'	-44.8± 2.4**
Dexamethasone	-42.2±2.6**	55 β	-37.4±7.1**
4 α	-0.6±5.1	59 β	-7.7± 6.8
4 β	-7.9±5.0	64 β	-32.5± 0.5**
5 β	-47.4±2.9**	64'	-41.3±-2.3**
10	-38.3±5.3**	65 β	-33.0± 3.3**
14 α'	5.7±1.9	66	-29.3± 6.3**
14 β	-8.7±7.2	69 β	0.7± 2.4
15 α	-39.5±1.8**	74 β	1.6±16.2
15 β	-41.0±2.6**	75 β	-10.0± 8.8
24 α	-3.7±4.5	84 α	-16.0± 2.9
25 α	-18.0±4.8*	84 β	-7.3± 3.8
29	-35.7±5.6**	85 α	-31.1± 2.2**
34 β	-21.3±3.9*	85 β	-7.8± 5.2
35 β	-21.9±4.2*	87	1.2± 6.1
44 β	-16.5±3.0*	89 α	-22.1± 6.0*
44'	3.3±4.7	89 β	-26.4± 2.2**
45 β	-28.1±3.5**	90	-13.1± 4.7

Test compound	Weight of granuloma
Control	0.0±5.1
White soft paraffin (base)	-0.7±7.1
Betamethasone valerate	-19.4±4.8
Dexamethasone	-55.4±5.7
105 β	-1.2±5.7
107 β	-6.3±5.5
109 β	-0.2±3.7

Figures indicate the per cent of inhibition over granuloma weights of the controls.

2. Croton oil-induced granuloma

1) Experimental method

5 [0151] Groups of 5 male Sprague-Dawley rats each weighing 160 - 180 g were used. Under ether anesthesia, the dorsum of animals was closely clipped, and air sac was formed by injecting air (20 ml) subcutaneously. Next day cotton seed oil containing 1% croton oil was injected into the air sac. Drugs to be tested were suspended in the cotton seed oil containing 1% croton oil, and administered. After 7 days, the blood was taken from the animal under ether anesthesia. Then, the granuloma pouch fluid (exudate) was collected, and the fluid volume was measured. The pouch wall
 10 formed around granuloma and thymus were also excised and weighed.

2) Results

15 [0152] Per cent of inhibition over the volume of pouch fluid, and wet weight of granuloma pouch as well as thymus of the control are shown in Tables 2 - 4.

Table 2

Effects of dexamethasone derivatives on croton oil-induced granuloma Effects on pouch fluid (exudate) volume				
	Test compound	0.01mg/rat	0.1mg/rat	1.0mg/rat
20	Betamethasone valerate	21.3±10.8	1.3±6.3	23.9±12.1
	91 β	25.3± 5.3	18.4±6.1	18.9± 8.8
	100 β	20.8±11.7	17.5±5.9	69.4± 6.7
	103 β	32.8± 9.6	24.8±4.8	43.2± 6.9
25	Test compound	0.01mg/rat	0.1mg/rat	1.0mg/rat
	Betamethasone valerate	-6.4±16.1	14.0± 6.5	41.0± 9.9
	Diflupredonate	17.4±13.5	65.3±12.1	96.2± 1.2
	Diflurasone acetate	-20.9±13.8	-14.5±11.6	14.3±15.1
	Diflucortolone valerate	27.3± 6.7	48.9± 2.9	90.8± 3.3
	105 β	-8.1± 9.4	24.8± 8.8	76.4± 4.3
	107 β	-28.5±18.8	-30.9±20.9	28.8±15.2
30	Test compound	0.01mg/rat	0.1mg/rat	1.0mg/rat
	109 β	-13.1±16.7	14.6± 9.4	37.5±11.9
35	Test compound	0.1mg/rat	1.0mg/rat	10.0mg/rat
	Betamethasone valerate	14.3±7.6	46.2±5.8	----
	Betamethasone acetate propionate	27.6±8.1	43.6±4.7	----
	Diflucortolone valerate	48.3±6.1	92.4±2.1	----
	109 β	26.6±4.2	61.3±2.9	90.8±1.6
40	110 β	34.4±8.0	73.6±2.1	97.2±0.5
	112 β	36.1±9.2	43.7±2.5	93.1±1.6
	113 β	90.5±6.6	97.1±0.5	97.5±0.7
	Figures indicate the per cent of inhibition over the pouch fluid volume of the control.			

Table 3

Effects of dexamethasone derivatives on croton oil-induced granuloma Effects on granuloma weight			
Test compound	0.01mg/rat	0.1mg/rat	1.0mg/rat
Betamethasone valerate	25.0±5.1	10.2± 5.2	18.7±11.7
91 β	17.1±6.7	6.9± 5.1	4.3± 8.2
100 β	11.0±6.5	4.1±11.3	60.5± 5.8
103 β	25.9±8.6	15.0± 7.0	34.5± 6.4
Test compound	0.01mg/rat	0.1mg/rat	1.0mg/rat
Betamethasone valerate	-7.0±14.3	0.4± 9.4	23.6±10.1
Diflupredonate	-11.0±23.1	35.0±10.3	78.8± 5.0
Diflurasone acetate	-13.1±13.3	4.0±10.5	11.7±12.4
Diflucortolone valerate	12.8± 5.1	22.1± 3.6	66.0± 7.1
105 β	-5.9±10.9	22.1± 3.7	53.0± 6.2
107 β	-21.2±19.2	-23.3±21.4	28.1±12.5
109 β	-21.3±13.5	6.0± 9.3	36.5±10.2
Test compound	0.1mg/rat	1.0mg/rat	10.0mg/rat
Betamethasone valerate	8.1± 7.0	36.4±4.4	----
Betamethasone acetate propionate	21.2± 6.4	26.0±6.9	----
Diflucortolone valerate	25.1± 5.0	66.4±3.3	----
109 β	13.5± 4.4	44.7±3.6	58.0±1.9
110 β	16.8± 7.1	58.7±1.4	70.3±1.9
112 β	15.9± 6.9	27.1±2.4	61.3±2.2
113 β	47.4±11.0	60.8±9.3	90.5±0.6

Table 4

Effects of dexamethasone derivatives on croton oil-induced granuloma Effects on thymus weight			
	Test compound	0.01mg/rat	0.1mg/rat
5	Betamethasone valerate	-0.5±5.8	7.3±4.1
10	91 β	2.1±3.7	7.4±2.8
15	100 β	6.3±4.8	0.1±4.5
20	103 β	21.5±5.7	11.2±3.1
25			4.3±3.9
30	Test compound	0.01mg/rat	0.1mg/rat
35	Betamethasone valerate	1.7± 6.3	13.5±5.8
40	Difluprednate	14.7±10.4	71.2±2.9
45	Diflurasone acetate	3.9± 9.0	32.4±4.5
50	Diflucortolone valerate	31.6± 6.4	70.6±3.4
55	105 β	-1.9± 7.8	-2.0±8.6
60	107 β	-4.2± 5.5	3.9±5.9
65	109 β	-2.7± 7.5	-6.0±9.6
70			3.4±8.6
75	Test compound	0.1mg/rat	1.0mg/rat
80	Betamethasone valerate	22.3± 1.6	50.1±6.0
85	Betamethasone acetate propionate	16.7±14.1	56.3±3.6
90	Diflucortolone valerate	80.1± 2.5	81.4±2.4
95	109 β	10.9± 8.6	17.7±4.6
100	110 β	20.9± 6.3	22.9±8.4
105	112 β	13.7± 7.3	20.5±5.7
110	113 β	78.9± 3.2	95.8±0.8
115			94.8±0.6
120	Figures indicate the per cent of inhibition over the control thymus weight.		

[0153] Results shown in Tables 2 - 4 confirmed that the compounds of the present invention have inhibitory effects on the growth of granuloma in rats.

[0154] That is, results in Tables 2 - 4 indicate that the compounds of the present invention have the following pharmacological properties.

- 1) Effects on thymus weight are significantly reduced with the glucosyl derivatives as compared with the non-glucosylated original compounds or the conventional anti-inflammatory drugs.
- 2) Reducing effects on the thymus atrophy were clearly observed with the glucosylated derivatives protected with toluoyl, benzoyl and chlorobenzoyl groups, but not with those protected with acetyl group.
- 3) Suppression effects of glucosyl derivatives on granuloma weights and pouch exudate volumes were lower than those of the non-glycosylated compounds, but more highly effective than those of the conventional drugs.

3. Inhibitory effects on croton oil-induced ear lobe edema

- 1) Experimental method

[0155] Groups of 10 male ddY mice each weighing about 25 g were used. Ointment to be tested (20 mg) was

rubbed in the right-side ear lobe, and, 30 min later, a drop of 4% croton oil dissolved in ether was applied to it. Thirty minute after that treatment, mice were sacrificed. Ear lobes on both sides were punched out in the size of 5-mm diameter, and weighed. Results were expressed by calculating the per cent of weight change of the right edema ear as compared with that of the untreated left ear, and compared with that of the control.

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2) Results

[0156] Per cent of inhibition of edema formation in experimental mice as compared with those of controls are shown in Tables 5 and 6.

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Table 5

5 Effects of dexamethasone derivatives on croton oil-induced ear
edema

	Test compound	Per cent of inhibition of ear edema (%)	Test compound	Per cent of inhibition of ear edema (%)
10	Control	0.0±5.3	45 β	24.6±6.3**
15	White soft paraffin (Base)	1.6±4.9	54'	25.7±4.1**
20	Betamethasone valerate	29.1±5.9**	54 β	13.2±5.1
25	Dexamethasone	32.9±3.5**	55 β	21.6±5.9*
30	4 α	24.1±4.9**	59 β	13.6±4.0
35	4 β	23.5±4.1**	64'	18.4±4.5*
40	5 β	19.6±3.3**	64 β	17.7±2.8**
45	10	27.5±5.9**	65 β	26.5±3.2**
50	14 α	9.0±4.9	66	18.3±3.6*
55	14 β	11.9±3.5	69 β	17.8±3.8*
60	15 α	27.5±3.6**	75 β	22.0±4.7**
65	15 β	34.0±4.1**	74 β	14.1±4.5
70	24 α	6.8±2.9	84 α	13.6±3.6*
75	25 α	24.9±5.5**	84 β	11.0±4.8
80	29	22.1±4.7**	85 α	26.5±4.4**
85	34 β	9.1±5.0	85 β	19.2±3.7**
90	35 β	29.0±3.0**	87	8.8±5.0
95	44'	7.9±7.2	89 α	22.5±5.2**
100	44 β	9.2±4.5	89 β	22.2±5.3**
105	45'	21.0±6.4*	90	15.6±6.6

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Figures indicate the per cent of inhibition over the edema formation in the control.

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Table 6

Effects of dexamethasone derivatives on croton oil-induced ear edema	
Test compound	Per cent of inhibition of ear edema (%)
Control	0.0±7.3
White soft paraffin (base)	7.4±6.3
Betamethasone valerate	24.9±3.5
Dexamethasone	32.9±3.5
91 β	32.9±7.8
94 β	35.1±4.1
97 β	36.6±5.1
100 β	40.5±4.7
105 β	42.0±2.9
107 β	41.4±6.1
109 β	38.6±9.2
114 β	49.8±9.7
115 β	23.3±2.1
117 β	24.2±6.3

Figures indicate the per cent inhibition to the edema formation in controls.

[0157] Results in Tables 5 and 6 confirmed that the compounds of the present invention have inhibitory effects on the croton oil-induced ear edema in mice.

4. Effects of 7-day ointment rubbing on organ weights

1) Experimental method

[0158] Groups of 5 male Sprague-Dawley rats each weighing 150 - 170 g were used. Under ether anesthesia, the dorsum of animals were closely clipped, and test drug (100 mg) was carefully rubbed in the clipped dorsal area for 30 seconds. Rats were slipped on plastic cage to prevent them from licking the drug-applied area. After the drug rubbing once daily for 7 days, on the 8th day rats were anesthetized with ether. Blood samples were collected, and thymus, spleen, and adrenal were excised and measured their wet weights. Furthermore, leukocyte number was counted with the blood samples collected. Results were expressed as the per cent of change of body weight on the 8th day as compared with that on the 1st day of rubbing. Similarly, the per cent of change in weights of thymus, spleen and adrenal on the 8th day as compared with that of the control animals were shown.

2. Results

[0159] Effects of 7-day ointment rubbing on weights of body, thymus, spleen and adrenal, and leukocyte counts are shown in Tables 7 and 8.

Table 7

5 Effects of 7-day rubbing of dexamethasone derivatives on body
weight, organ weight and leukocyte count

	Test compound	Body weight	Adrenal weight	Thymus weight	Spleen weight	Leukocyte count
10	Normal animal	23.2 ± 1.7	3.0 ± 5.6	0.0 ± 2.2	3.0 ± 3.4	0.0 ± 6.3
	White soft paraffin (base)	22.3 ± 0.6	-1.8 ± 4.5	-6.0 ± 7.5	13.1 ± 5.5	-20.3 ± 11.9
15	Betamethasone valerate	23.8 ± 2.7	-12.8 ± 2.2"	-23.3 ± 3.4"	-10.9 ± 5.0	1.5 ± 3.0
	Dexamethasone	-8.7 ± 1.4"	-48.5 ± 1.4"	-91.5 ± 0.5"	-70.0 ± 3.5"	-46.5 ± 12.1"
20	4 α	27.2 ± 0.9'	-13.8 ± 2.3'	3.1 ± 8.9	9.9 ± 6.0	3.2 ± 4.5
	4 β	21.4 ± 1.6"	-15.3 ± 3.0'	0.6 ± 5.9	1.9 ± 4.3	19.0 ± 4.7
	5 β	0.7 ± 1.4"	-49.6 ± 3.2"	-85.7 ± 2.6"	-56.0 ± 1.6"	-46.6 ± 3.2"
25	10	-2.7 ± 2.6"	-53.8 ± 3.5"	-85.5 ± 3.8"	-68.5 ± 2.8"	-54.9 ± 4.3"
	14 α	25.2 ± 0.8"	-11.0 ± 5.7	-10.7 ± 8.5	-5.5 ± 7.1	-21.8 ± 0.5
	14 β	25.3 ± 1.6'	-9.5 ± 4.8	-12.0 ± 2.2	0.5 ± 5.1	-0.6 ± 6.1
	15 α	8.3 ± 1.0"	-48.3 ± 2.9"	-82.2 ± 3.3"	-35.7 ± 2.3"	-22.6 ± 7.4'
	15 β	4.6 ± 0.9"	-47.1 ± 1.9"	-86.0 ± 1.4"	-43.2 ± 2.1"	-37.0 ± 6.9"
30	24 α	22.7 ± 1.9"	-7.8 ± 8.3	-15.1 ± 11.4	-2.0 ± 7.3	-4.3 ± 9.4
	25 α	16.1 ± 1.7'	-24.4 ± 3.4"	-32.6 ± 7.4"	-18.2 ± 7.2"	-0.7 ± 9.0
	29	-1.1 ± 2.0"	-46.0 ± 2.4"	-89.8 ± 2.2"	-59.5 ± 1.6"	-53.5 ± 4.9"
	34 β	11.8 ± 1.0"	-37.4 ± 3.9"	-66.4 ± 1.1"	-37.2 ± 1.8"	-43.7 ± 6.7"
	35 β	10.5 ± 2.8"	-29.9 ± 5.0"	-61.9 ± 3.1"	-28.7 ± 5.5"	-36.4 ± 4.7"
35	44'	22.7 ± 1.1"	-19.6 ± 5.5"	-17.9 ± 3.3"	-11.5 ± 4.8	-23.0 ± 5.1
	44 β	12.4 ± 2.7"	-33.0 ± 4.6"	-57.2 ± 9.5"	-35.4 ± 4.9"	-20.7 ± 7.0
	45'	22.9 ± 1.7	-15.4 ± 3.2'	-6.8 ± 4.0	-0.1 ± 5.1	6.6 ± 15.1
	45 β	13.3 ± 3.1'	-37.6 ± 2.8"	-55.1 ± 7.9"	-24.2 ± 5.3"	-22.3 ± 4.5"
	54'	-0.8 ± 1.6"	-50.1 ± 3.0"	-87.6 ± 3.0"	-63.2 ± 3.1"	-57.2 ± 6.0"
40	54 β	13.6 ± 1.6"	-41.7 ± 5.1"	-64.6 ± 6.3"	-41.3 ± 1.7"	-35.1 ± 4.8"
	55 β	12.4 ± 2.7"	-42.5 ± 3.7"	-69.9 ± 5.5"	-26.8 ± 11.0"	-43.3 ± 4.4"
	59 β	24.4 ± 1.2"	-17.4 ± 3.9'	-17.5 ± 10.3	0.0 ± 6.6	11.8 ± 5.7
	64'	-0.9 ± 2.0"	-50.1 ± 2.3"	-89.6 ± 2.0"	-61.9 ± 2.6"	-57.2 ± 2.9"
	64 β	7.8 ± 1.5"	-46.0 ± 4.1"	-86.5 ± 1.4"	-47.6 ± 2.0"	-48.3 ± 4.6"
45	65 β	13.9 ± 2.1"	-32.0 ± 2.9"	-47.1 ± 9.9"	-21.3 ± 4.0"	-20.3 ± 19.7
	66	14.3 ± 1.6"	-28.8 ± 3.0"	-39.0 ± 5.2"	-19.4 ± 2.2"	-25.9 ± 13.8
	69 β	26.3 ± 2.0	-3.9 ± 3.9	-16.5 ± 8.6	-4.4 ± 4.7	6.9 ± 9.3
	74 β	19.4 ± 2.1"	-24.6 ± 3.7"	-26.3 ± 5.6"	-9.1 ± 4.6	6.5 ± 8.4
50	75 β	22.5 ± 2.5	-48.9 ± 10.6"	-21.3 ± 8.9"	3.5 ± 4.2	19.3 ± 9.5
	84 α	24.8 ± 1.7'	-19.7 ± 3.3"	-16.4 ± 6.2	-15.2 ± 3.6"	-5.5 ± 13.5
	84 β	26.6 ± 3.1	-17.6 ± 2.1"	-13.5 ± 4.9	-5.0 ± 11.1	2.3 ± 13.3
	85 α	12.9 ± 2.7"	-40.9 ± 2.0"	-58.2 ± 6.7"	-27.8 ± 3.5"	-25.2 ± 3.3"
	85 β	14.1 ± 2.3'	-53.4 ± 5.2"	-53.1 ± 7.5"	-16.1 ± 8.9	-32.5 ± 9.4"
	87	23.5 ± 1.5"	-12.1 ± 3.5"	-10.8 ± 5.8	-1.3 ± 4.6	-10.3 ± 12.5
	89 α	19.6 ± 1.5	-22.7 ± 1.8"	-18.5 ± 6.9	-7.2 ± 2.9	18.7 ± 8.7
	89 β	16.7 ± 1.8	-22.7 ± 3.1"	-33.1 ± 8.8"	-13.6 ± 2.7"	-6.6 ± 6.8
	90	21.7 ± 1.6	-22.9 ± 3.7"	-9.2 ± 6.3	0.1 ± 4.4	12.8 ± 8.0

Table 8

Test Compound	Body Weight	Adrenal weight	Thymus weight	Spleen weight	Leukocyte count
Normal animal	30.5±1.3	0.0±2.4	0.0±4.1	0.0±5.4	0.0±8.6
White soft paraffin (base)	28.2±0.6	-1.8±4.5	-6.0±7.5	13.1±5.5	-20.3±11.9
Betamethasone valerate	18.1±1.6	-26.9±5.5	-57.2±5.1	-28.8±3.7	-44.7±3.8
Dexamethasone	-8.8±3.4	-49.2±3.7	-91.9±0.9	-71.6±2.1	-61.1±3.3
105 β	22.4±1.0	0.7±4.5	0.6±4.4	6.7±2.6	-10.6±6.2
107 β	27.6±2.2	-5.7±2.6	2.8±6.7	8.8±3.6	-20.3±14.4
109 β	27.6±3.2	-0.8±1.8	14.1±5.9	-0.9±5.7	-29.2±9.9

[0160] Results shown in Tables 7 and 8 confirmed that the compounds of the present invention are less toxic and pharmacologically more safe than dexamethasone.

[0161] As aforementioned, a series of steroid compounds of the present invention have the pharmacological effects shown in Tables 2 - 8, respectively. Among them, particularly, glycosyl steroid derivatives with Tol-protecting group including glucosyl dexamethasone protected with Tol group and β -galacturonyldexamethasone protected with Tol group not only have suppressing effects on granuloma growth and croton oil-induced ear edema, but also they are less toxic and highly more safe.

Example 13

Synthesis of glucosylbetamethasone (*p*-toluoyl derivative) (modified method) (Fig. 13)

1) Synthesis of glucosylbetamethasone (*p*-toluoyl derivative) (91) 3 + 86 → 91

[0162] Betamethasone (86) (1.28 g) was dissolved in acetonitrile (85 ml), and to this solution were added molecular sieve 3A (1.80 g) and silver triflate (1.62 g). To this mixture was added, under an argon atmosphere and at 0 - 5°C, a solution of a glucose bromide (3) (4.65 g) dissolved in acetonitrile (45 ml). While the reaction temperature was slowly raised to room temperature, the resulting mixture was stirred for 6 h. To this mixture was further added silver triflate (1.62 g), and the resulting mixture was stirred at room temperature for 19 h. The reaction solution was filtered, and the solvent was distilled off from the filtrate *in vacuo*. The residue was dissolved in chloroform, and the solution was washed with saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 5:4) to give white powder (2.62 g). This powder was further purified by HPLC using a reversed phase partition column (acetonitrile-water) to give β -anomer (91 β) as white powder [2.05 g (yield 61.1%)].

Example 14

Synthesis of glucosylbetamethasone (*o*-toluoyl derivative) (Fig. 14)

1) Toluoylation of glucose 1 → 92

[0163] D-(+)-Glucose (1) (1.21 g) was dissolved in chloroform (24 ml), and to this solution were added *p*-toluoyl chloride (8.85 ml) and pyridine (5.49 ml) drop-wise at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, the reaction mixture was stirred for 4 h. The reaction solution was poured into ice-water, and extracted with chloroform. The organic layer was washed successively with saturated solutions of copper sulfate, sodium bicarbonate, and sodium chloride. After the solution was dried over anhydrous magnesium sulfate, the solvent was evaporated from the solution *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 6:1) to give 92 as white powder [5.16 g (quant.)].

Compound 92

[0164]

5 $C_{46}H_{42}O_{11}$ MW = 770.881
 1H -NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

8 ; 2.578, 2.561, 2.492, 2.439, 2.352
(15H, 5s, $CH_3C_6H_4CO^-$)
10 6.877 (1H, d, J = 3.66, H-1)
8.061, 7.961, 7.887, 7.831, 7.790
(5H, 5d, J = 8.06, $CH_3C_6H_4CO^-$)

2) Bromination of glucose (*o*-toluoyl derivative) 92 → 93

15 [0165] 92 (2.84 g) was dissolved in chloroform (13 ml), and to this solution was added hydrogen bromide-acetic acid solution (7.7 ml) at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 3 h. After the unreacted bromine was removed with an argon stream, the solvent was distilled off *in vacuo*. The residue was dissolved in chloroform, and the solution was washed cold saturated sodium bicarbonate solution.
20 After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo* to give 93 as pale yellow powder [2.44 g (yield 92.6%)].

Compound 93

[0166]

25 $C_{38}H_{35}O_9Br$ MW = 715.593
 1H -NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

30 8 ; 2.611, 2.553, 2.451, 2.340
(12H, 4s, $CH_3C_6H_4CO^-$)
6.890 (1H, d, J = 4.03, H-1)
8.002, 7.974, 7.912, 7.734
(4H, 4d, J = 8.06, $CH_3C_6H_4CO^-$)

35 3) Synthesis of glucosylbetamethasone (*o*-toluoyl derivative)

93+86→94

40 [0167] Betamethasone (86) (350 mg) was dissolved in acetonitrile (23 ml), and to this solution were added molecular sieve 3A (460 mg) and silver triflate (437 mg). To this mixture was added, under an argon atmosphere and at 0 - 5°C, a bromide of glucose (*o*-toluoyl derivative) (93) (1.22 g) dissolved in acetonitrile (12 ml). While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 6 h. To this mixture was further added silver triflate (437 mg), and the resulting mixture was stirred at room temperature for 17 h. The reaction solution was filtered, and the solvent was distilled off from the filtrate *in vacuo*. The residue was dissolved in chloroform, and washed with saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 5:4) to give white powder (723.8 mg). This powder was further purified by HPLC using a reversed phase partition column chromatography (acetonitrile-water) to give 94β as white powder [450.4 mg (yield 49.2%)].

50 50 Compound 94β

[0168]

55 $C_{60}H_{63}O_{14}F$ MW = 1027.15
 1H -NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 2.574, 2.482, 2.436, 2.277 (12H, 4s, $CH_3C_6H_4CO^-$)

4.119-4.081 (1H, m, H-5)
 4.578 (2H, d, J = 4.39, H-6, 6')
 5.043 (1H, d, J = 8.06, H-1)
 5.542 (1H, dd, J = 9.53, H-2)
 5.642 (1H, t, H-4)
 5.898 (1H, t, H-3)
 6.113 (1H, s, Bet-4)
 6.319 (1H, d, Bet-1)
 7.965, 7.840, 7.755
 10 (4H, 3d, J = 6.96, $\text{CH}_3\text{C}_6\text{H}_4\text{CO}-$)

FAB(+)MS calcd. 1026.42 ; 1049(M+Na)⁺
 MP : 124 - 127°C
 IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} 1734(C = O position-20), 1665(C = O position-3)

Example 15

Synthesis of glucosylbetamethasone (*m*-toluoyl derivative) (Fig. 15)

20 1) *m*-Toluoylation of glucose 1 → 95

[0169] D-(+)-Glucose (1) (1.26 g) was dissolved in chloroform (24 ml), and to this solution were added *m*-toluoyl chloride (9.20 ml) and pyridine (5.65 ml) at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 3 h. The reaction solution was poured into ice-water, and extracted with chloroform. The organic layer was washed successively with saturated solutions of copper sulfate, sodium bicarbonate, and sodium chloride. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 5:1) to give 95 as white powder [5.49 g (quant.)].

30 Compound 95

[0170]

$\text{C}_{46}\text{H}_{42}\text{O}_{11}$ MW = 770.881
 35 $^1\text{H-NMR}$ [500MHz, CDCl_3 , Ref = 0.000ppm(TMS)]

δ : 2.463, 2.372, 2.328, 2.293, 2.248
 (15H, 5s, $\text{CH}_3\text{C}_6\text{H}_4\text{CO}-$)
 6.834 (1H, d, J = 4.03, H-1)

40 2) Bromination of glucose (*m*-toluoyl derivative) (97) 95 → 96

[0171] (95) (2.64 mg) was dissolved in chloroform (12 ml), and to this solution was added hydrogen bromide-acetic acid solution (5.2 ml) at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 5 h. After the unreacted bromine was removed with an argon stream, the solvent was distilled off *in vacuo*. The residual material was dissolved in chloroform, and washed with cold saturated sodium bicarbonate solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo* to give 96 as white powder [2.27 g (yield 92.5%)].

50 Compound 96

[0172]

$\text{C}_{38}\text{H}_{35}\text{O}_9\text{Br}$ MW = 715.593
 55 $^1\text{H-NMR}$ [500MHz, CDCl_3 , Ref = 0.000ppm(TMS)]

δ : 2.401, 2.353, 2.338, 2.290(12H, 4s, $\text{CH}_3\text{C}_6\text{H}_4\text{CO}-$)
 6.874 (1H, d, J = 4.03, H-1)

7.865, 7.799, 7.755, 7.684
(8H, 4d, J = 7.70, $\text{CH}_3\text{C}_6\text{H}_4\text{CO}-$)

3) Synthesis of glucosylbetamethasone (*m*-toluoyl derivative) (97) 96+86→97

[0173] Betamethasone (86) (334 mg) was dissolved in acetonitrile (23 ml), and to this solution were added molecular sieve 3A (460 mg) and silver triflate (437 mg). To this mixture was added, under an argon atmosphere and at 0 - 5°C, a bromide of glucose (*m*-toluoyl derivative) (96) (1.22 mg) dissolved in acetonitrile (12 ml). While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 3 h. To this mixture was further added silver triflate (437 mg), and the resulting mixture was stirred at room temperature overnight. The reaction solution was filtered, and the solvent was distilled off from the mother liquor *in vacuo*. The residual material was dissolved in chloroform, and the solution was washed with saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 5:4) to give white powder (819 mg). A portion of this product (300 mg) was further purified by HPLC using a reversed phase partition column chromatography (acetonitrile-water) to give β -anomer (97B) as white powder [212.9 mg (yield 66.5%)].

Compound 97B

20 [0174]

$\text{C}_{60}\text{H}_{63}\text{O}_{14}\text{F}$ MW = 1027.15
 $^1\text{H-NMR}$ [500MHz, CDCl_3 , Ref = 0.000ppm(TMS)]

25 δ : 2.338, 2.317, 2.294, 2.272 (12H, 4s, $\text{CH}_3\text{C}_6\text{H}_4\text{CO}-$)
4.133-4.096 (1H, m, H-5)
5.035 (1H, d, J = 8.06, H-1)
5.541 (1H, dd, J = 9.53, H-2)
5.656 (1H, t, H-4)
30 5.833 (1H, t, H-3)
6.135 (1H, s, Bet-4)
6.344 (1H, d, J = 9.89, Bet-1)
7.786, 7.738, 7.705, 7.642
(4H, 3d, J = 7.69, $\text{CH}_3\text{C}_6\text{H}_4\text{CO}-$)

35 FAB(+)MS calcd. 1026.42 ; 1049(M+Na)⁺
MP : 125 - 128°C
IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} 1735(C = O position-20), 1665(C = O position-3)

40 Example 16

Synthesis of glucosylbetamethasone (benzoyl derivative) (Fig. 16)

1) Benzoylation of glucose 1→98

45 [0175] D-(+)-Glucose (1) (1.30 g) was dissolved in chloroform (24 ml), and to this solution were added benzoyl chloride (8.3 ml) and pyridine (5.8 ml) drop-wise at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, this mixture was stirred for 4 h. The reaction solution was poured into ice-water, and extracted with chloroform. The organic layer was washed successively with saturated solutions of copper sulfate, sodium bicarbonate, and sodium 50 chloride. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1) to give 98 as white powder [7.26 g (theoretical)].

Compound 98

55 [0176]

$\text{C}_{41}\text{H}_{32}\text{O}_{11}$ MW = 700.693

¹H-NMR [500MHz, CDCl₃, Ref = 0.000ppm(TMS)]

5 δ : 5.683 (1H, dd, J = 10.26, H-2)
 5.859 (1H, t, H-4)
 6.319 (1H, t, H-3)
 6.853 (1H, d, J = 4.03, H-1)
 8.167, 8.026, 7.946, 7.874 (8H, 4d, J = 8.43, C₆H₅CO-)

2) Bromination of glucose (benzoyl derivative) 98→99

10 [0177] 98 (3.89 g) was dissolved in chloroform (19 ml), and to this solution was added hydrogen bromide-acetic acid solution (8.5 ml) at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 4 h. After the unreacted bromine was removed with an argon stream, the solvent was evaporated from the reaction mixture *in vacuo*. The residue was dissolved in chloroform, and washed with cold saturated sodium bicarbonate solution. After the solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo* to give 99 as pale yellow powder [2.80 g (yield 76.4%)].

Compound 99

20 [0178]

C₃₄H₂₇O₉Br MW = 659.485
¹H-NMR [500MHz, CDCl₃, Ref = 0.000ppm(TMS)]

25 δ : 4.514 (1H, dd, J = 12.82, H-6)
 4.667 (1H, dd, J = 4.77, H-6)
 4.751-4.716 (1H, m, H-5)
 5.328 (1H, dd, J = 9.89, H-2)
 5.818 (1H, t, H-4)
 6.263 (1H, t, H-3)
 6.865 (1H, d, J = 4.03, H-1)
 8.068, 8.002, 7.952, 7.874 (8H, 4d, J = 8.06, C₆H₅CO-)

3) Synthesis of glucosylbetamethasone (benzoyl derivative) 100

35 99+86→100

40 [0179] Betamethasone (86) (510 mg) was dissolved in acetonitrile (35 ml), and to this solution were added molecular sieve 3A (700 mg) and silver triflate (668 mg). To this mixture was added, under an argon atmosphere and at 0 - 5°C, a glucose bromide (benzoyl derivative) (99) (1.72 g) dissolved in acetonitrile (18 ml). While the reaction mixture was slowly raised to room temperature, the reaction mixture was stirred for 5 h. To this mixture was further added silver triflate (668 mg), and the resulting mixture was stirred at room temperature for 18 h. The reaction solution was filtered, and the solvent was distilled off from the mother liquor *in vacuo*. The residue thus obtained was dissolved in chloroform, and was washed with saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 5:4) to give white powder (1.24 g), which was further purified by HPLC using a reversed phase partition chromatography (acetonitrile-water) to give β-anomer (100β) as white powder [813 mg (yield 64.4%)].

50 Compound 100β

[0180]

55 C₅₆H₅₅O₁₄F MW = 971.04
¹H-NMR [500MHz, CDCl₃, Ref = 0.000ppm(TMS)]

δ : 4.149-4.112 (1H, m, H-5) 5.064 (1H, d, J = 8.06, H-1)
 5.562 (1H, dd, J = 9.53, H-2)

5 5.695 (1H, t, H-4)
 5.917 (1H, t, H-3)
 6.126 (1H, s, Bet-4)
 6.339 (1H, d, Bet-1)
 7.990, 7.947, 7.926, 7.832 (8H, 4d, J = 8.43, C_6H_5CO-)

10 FAB(+)MS calcd. 970.36 ; 993 (M+Na)⁺
 MP : 142 - 145°C
 IR ν_{max}^{KBr} cm⁻¹ 1734(C = O position-20), 1665(C = O position-3)

15 Example 17

Synthesis of gulcosylbetamethasone (benzyl derivative) (Fig. 17)

15 1) S-Methylation of glucose 8 → 101

[0181] β -D-Glucose-penta-O-acetate (8) (5 g) and tributyltin methylsulfide (6.5 g) were suspended in dichloroethane (40 ml), and to this suspension was added, under ice-cooling, tin(IV) chloride (1.94 ml). The resulting mixture was stirred at 0°C for 5 h. After the reaction mixture was diluted with chloroform, a potassium fluoride solution was added to the above mixture, and stirred at room temperature. The reaction solution was filtered through celite, and the mother liquor was washed successively with saturated sodium bicarbonate solution, water, and saturated sodium chloride solution. After the organic layer was dried over anhydrous magnesium sulfate, the solvent was distilled off from the solution *in vacuo*. The residual material thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 3:2) to give 101 as white powder [4.5 g (yield 93.2%)].

25 Compound 101

[0182]

30 $C_{15}H_{22}O_9S$ MW = 378.39
 1H-NMR [500MHz, CDCl₃, Ref = 0.000ppm(TMS)]

35 8 : 2.086, 2.069, 2.030, 2.013 (12H, 4s; CH_3COO-)
 2.173 (3H, s, CH_3S-)
 3.754-3.720 (1H, m, H-5)
 4.151 (1H, dd, J = 12.46, H-6)
 4.256 (1H, dd, J = 5.13, H-6')
 4.399 (1H, d, J = 9.90, H-1)
 5.107-5.056 (2H, m, H-2, H-4)
 5.235 (1H, t, J = 9.52, H-3)

40 2) Benzylation of glucose (S-methyl derivative) 101 → 102

[0183] Glucose (S-methyl derivative) (101) (400 mg) was dissolved in methanol (6 ml), and to this solution was added 1 M sodium methoxide (0.5 ml) at 0 - 5°C. The mixture was stirred at room temperature for 5 h. After the solvent was distilled off from the reaction mixture *in vacuo*, the residual material was dissolved in DMF (9 ml), and to this solution were added benzyl bromide (1.45 g) at 0°C, followed by sodium hydride (0.4 mg). The resulting mixture was stirred for 3 h, while it was allowed to warm up slowly to room temperature. Then, to this reaction mixture was added methanol under ice-cooling, and the resulting mixture was evaporated *in vacuo*. To the residue thus obtained was added diethyl ether, and the solution was washed with saturated sodium chloride solution. After the solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. The residual material thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 7:1) to give 102 as white powder [445.2 mg (yield 73.8%)].

45 Compound 102

[0184]

55 $C_{35}H_{38}O_5S$ MW = 570.75

¹H-NMR [500MHz, CDCl₃, Ref = 0.000ppm(TMS)]

5 δ : 2.244 (3H, s, CH₃S-)
 4.362 (1H, d, J = 9.52, H-1)

3) Synthesis of glucosylbetamethasone (benzyl derivative) 103 102 + 86 → 103

[0185] Betamethasone (86) (114 mg) and glucose (O-benzyl, SMe-derivative) (102) (200 mg) were dissolved in chloroform (6 ml), and to this solution were added molecular sieve 4A (80 mg), followed by methyl triflate (75 µl) at 10 - 20°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 5 h. The reaction solution was basified by the addition of triethylamine, filtered, and the solvent was distilled off from the mother liquor *in vacuo*. The residue was then diluted with chloroform, and the resulting solution was washed with saturated solutions of sodium bicarbonate and sodium chloride. After the solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. Residual material thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 5:4) to give 103 (mixture of α-, β-anomers, α:β = 3:1) as white powder [200 mg (yield 75.4%)].

Compound 103

[0186]

20 C₅₆H₆₃O₁₀F MW = 915.11
¹H-NMR [500MHz, CDCl₃, Ref = 0.000ppm(TMS)]

25 δ : 3.492 (0.25H, dd, H-2, β)
 3.598 (0.75H, dd, H-2, α)
 4.504 (0.25H, d, J = 7.70, H-1, β)
 4.823 (0.75H, d, J = 4.03, H-1, α)
 6.110 (0.25H, s, Bet-4, β)
 6.143 (0.75H, s, Bet-4, α)
30 6.310 (0.25H, s, Bet-1, β)
 6.338 (0.75H, s, Bet-1, α)

FAB(+)MS calcd., 914.44 ; 915(M+H)⁺

MP : 80 - 83°C

35 IR ν_{max}^{KBr} cm⁻¹ 1725(C = O position-20), 1663(C = O position-3)

Examples 18 - 23

Syntheses of glucosyldifluorosteroids (Figs. 18 - 23)

40 1) Synthesis of glucosyldiflupredonate (*p*-toluoyl derivative) 105

3 + 104 → 105

45 [0187] Diflupredonate hydrolysate (104) (315 mg) was dissolved in acetonitrile (18 ml), and to this solution were added molecular sieve 3A (439 mg) and silver triflate (409 mg). To this mixture was added, under an argon atmosphere and at 0 - 5°C, a glucose bromide (3) (1.14 g) dissolved in acetonitrile (18 ml). While the reaction temperature was raised slowly to room temperature, the resulting mixture was stirred for 2 h. To this mixture was further added silver triflate (409 mg), and the resulting mixture was stirred at room temperature for 18 h. After the reaction solution was filtered, the solvent of the mother liquor was evaporated *in vacuo*. The residue was dissolved in chloroform, and washed with saturated sodium chloride solution. After the solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1) to give white powder (870 mg). This product was further purified by HPLC using a reversed phase partition column (acetonitrile-water) to give β-anomer (105β) as white powder [641 mg (yield 78.2%)].

55

Compound 105B

[0188]

5 $C_{59}H_{60}O_{14}F_2$ MW = 1031.11
 1H -NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

8 : 2.420, 2.371, 2.340, 2.296(12H, 4s, $CH_3C_6H_4O$ -)
4.085-4.047 (1H, m, H-5)

10 4.561 (1H, dd, H-6)
4.792 (1H, dd, H-6')
4.889 (1H, d, J = 8.06, H-1)
5.454 (1H, dd, H-2)
5.633 (1H, t, H-3)
5.913 (1H, t, H-4)
7.869, 7.849, 7.828, 7.740
(8H, 4d, J = 8.43, $CH_3C_6H_4O$ -)

FAB(+)MS calcd. 1030.4 ; 1031(M+H)⁺, 1013(M-H₂O)⁺
20 MP : 152 - 155°C
IR ν_{max}^{KBr} cm⁻¹ 1733(C = O position-20), 1630(C = O position-3)

2) Synthesis of glucosyldiflorasone (*p*-toluoyl derivative) 10725 3 + 106 → 107

[0189] Hydrolysate of diflorasone (*p*-toluoyl derivative) (106) (206 mg) and a glucose bromide (3) (720 mg) were dissolved in a mixture of acetonitrile (3 ml) and cyanoethane (5 ml). To this solution was added molecular sieve 3A (1.0 g), and the mixture was stirred at room temperature for 3 h. This mixture was cooled to 0°C, and to the cooled mixture was added silver triflate (262 mg) dissolved in cyanoethane (1 ml). The resulting mixture was stirred for 20 h, while the reaction temperature was slowly raised to room temperature under an argon atmosphere. The reaction solution was diluted with chloroform, filtered through celite, and the mother liquor was washed with saturated sodium bicarbonate solution and then with saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 7:3) to give white powder (317 mg). This product was further purified by HPLC using reversed phase partition column (acetonitrile-water) to give β -anomer (107B) as white powder [231 mg (yield 44.4%)].

Compound 107B

40

[0190]

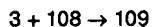
$C_{60}H_{62}O_{14}F_2$ MW = 1045.14
 1H -NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

45 δ : 2.387, 2.354, 2.351, 2.291 (12H, 4s, $CH_3C_6H_4O$ -)
4.120-4.084 (1H, m, H-5)
4.278 (1H, t, H-6)
4.582 (1H, t, H-6')
50 4.999 (1H, d, J = 8.06, H-1)
5.516 (1H, dd, H-2)
5.644 (1H, t, H-4)
5.873 (1H, t, H-3)
6.358 (1H, d, Diflora-1)
55 6.427 (1H, s, Diflora-4)
7.860, 7.830, 7.786, 7.717
(8H, 4d, J = 8.06, $CH_3C_6H_4O$ -)

FAB(+)MS calcd. 1044.41 ; 1045(M+H)⁺, 1067(M+Na)⁺,
 IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹ 1733(C = O position-20), 1671(C = O position-3)

3) Glucosyldiflucortolone (*p*-toluoyl derivative) 109

5



[0191] Hydrolysate of diflucortolone (108) (200 mg) was dissolved in acetonitrile (2 ml), and to this solution was added molecular sieve 3A (2 g). The mixture was stirred for 30 min. To this mixture were added, under an argon atmosphere and at 0 - 5°C, a glucose bromide (3) (725 mg) dissolved in acetonitrile (1 ml) and silver triflate (261 mg), and the resulting mixture was stirred for 2.5 h, while the reaction temperature was raised slowly to room temperature. After the reaction solution was filtered, the solvent was distilled off from the mother liquor *in vacuo*, and the residue was dissolved in ethyl acetate. The solution was washed with saturated sodium bicarbonate solution, then with saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. After the solvent was distilled off *in vacuo*, the residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 4:1) to give white powder (379 mg). A 370-mg portion of the product was further purified by HPLC using a reversed phase partition column (acetonitrile-water) to give β -anomer (109 β) as white powder [289 mg (yield 55.1%)].

Compound 109 β

20

[0192]

25

$\text{C}_{60}\text{H}_{62}\text{O}_{13}\text{F}_2$ MW = 1029.14
¹H-NMR [500MHz, CDCl₃, Ref = 0.000ppm(TMS)]

25

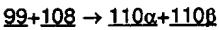
δ : 2.421, 2.364, 2.341, 2.293 (12H, 4s, CH₃C₆H₄O-)
 4.070-4.033 (1H, m, H-5)
 4.972 (1H, d, J = 8.06, H-1)
 5.478 (1H, dd, H-2)
 5.639 (1H, t, H-3)
 5.884 (1H, t, H-4)
 6.370 (1H, d, Difluco-1)
 6.437 (1H, s, Difluco-4)
 7.872, 7.831, 7.822, 7.729
 (8H, 4d, J = 8.06, CH₃C₆H₄O-)

35

FAB(+)MS calcd. 1028.4 ; 1029(M+H)⁺
 MP : 144 - 147°C
 IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹ 1734(C = O position-20), 1672(C = O position-3)

40

4) Synthesis of glucosyldiflucortolone (benzoyl derivative)



[0193] Hydrolysate of diflucortolone (108) [299.1 mg (0.758 mmol)] was dissolved in acetonitrile (20 ml), and to this solution were added molecular sieve 3A (about 700 mg) and silver triflate [390.6 mg (1.52 mmol)]. The mixture was stirred for 1 h. To this mixture was added, under an argon atmosphere and at 0°C, a benzoylglucose bromide (99) [1.0 g (1.52 mmol)] dissolved in acetonitrile (10 ml). While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 2 h. To this mixture was further added silver triflate (390.6 mg), and the resulting mixture was stirred at room temperature for 14 h. To this mixture was further added silver triflate (390.6 mg), and the resulting mixture was stirred at room temperature for 4 h. After the reaction solution was filtered, the solvent was distilled off from the filtrate *in vacuo*. The residue thus obtained was dissolved in chloroform, and the solution was washed with saturated sodium chloride solution. After the solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (ethyl acetate:hexane = 2:3 → 4:5) to give fractions containing the desired product (360.2 mg). This product was further purified by HPLC using a reversed phase partition column (water-acetonitrile) to give α -anomer (110 α) [19.9 mg (yield 2.7%)] and β -anomer (110 β) [249.9 mg (yield 33.9%)], respectively, both as white powder.

Compound 110 α

[0194]

5 C₅₆H₅₄F₂O₁₃ MW = 972.35
 MP : 135 - 138°C
 FAB(+)MS : 955(M-H₂O)⁺, 973(M+H)⁺, 995(M+Na)⁺
 IR ν _{max}^{KBr} cm⁻¹ : 3448(O-H), 1731(COPh), 1671(C=O 3-position), 1616 and 1603(C=C)
¹H-NMR [500MHz, CDCl₃, Ref = 0.000ppm(TMS)]

10 δ : 7.169(1H, d, J_{2,1} = 10.3, H-2)
 6.437(1H, d, J_{4,1} = 1.8, H-4)
 6.408(1H, dd, H-1)
 6.250(1H, t, J_{3,2} = 9.9, J_{3,4} = 9.9, H-3_{Glc})
 15 5.780(1H, t, J_{4,5} = 10.3, H-4_{Glc})
 5.338(1H, d, J_{1,2} = 3.7, H-1_{Glc})
 5.223(1H, dd, H-2_{Glc})
 4.917(1H, dd, H_{6,5} = 3.3, J_{6,6'} = 12.5, H-6_{Glc})
 4.657(1H, ddd, J_{6,6'} = 2.6, H-5_{Glc})
 20 4.296(1H, dd, H-6'_{Glc})
 4.249(1H, d, J_{gem} = 17.6, H-21)
 4.231(1H, d, H-21')
 1.553(3H, s, H-19)
 1.077(3H, s, H-18)
 25 0.968(3H, d, J_{16CH3,16} = 7.0, 16-CH₃)

Compound 110 β

[0195]

30 C₅₆H₅₄F₂O₁₃ MW = 972.35
 MP : 140 - 145°C
 FAB(+)MS : 955(M-H₂O)⁺, 973(M+H)⁺, 995(M+Na)⁺
 IR ν _{max}^{KBr} cm⁻¹ : 3440(O-H), 1731(COPh), 1671(C=O position-3), 1604(C=C)
¹H-NMR [500MHz, CDCl₃, Ref = 0.000ppm(TMS)]

35 δ : 7.115(1H, dd, J_{2,1} = 10.3, H-2)
 6.438(1H, d, H_{4,1} = 1.8, H-4)
 6.374(1H, dd, H-1)
 40 5.927(1H, t, J_{3,2} = 9.9, J_{3,4} = 9.9, H-3_{Glc})
 5.704(1H, t, J_{4,5} = 9.9, H-4_{Glc})
 5.519(1H, dd, J_{2,1} = 7.7, H-2_{Glc})
 5.038(1H, d, H-1_{Glc})
 4.691(2H, dd, J_{6,5} = 4.0; H-6_{Glc})
 45 4.268(1H, d, J_{gem} = 16.9, H-21)
 4.133(1H, d, H-21')
 4.084(1H, td, H-5_{Glc})
 1.558(3H, s, H-19)
 0.900(3H, s, H-18)
 50 0.821(3H, d, J_{16CH3,16} = 7.0, 16-CH₃)

5) Synthesis of glucosyldiflucortolone (*p*-chlorobenzoyl derivative) 112109 → 111 → 112

55 [0196] Glucosyldiflucortolone (*p*-toluoyl derivative; 109) (1.34 g) was dissolved in chloroform (40 ml), and to this solution was added, under ice-cooling, 1 M sodium methoxide (1.04 ml). While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 1 h. To this reaction solution was added methanol (30 ml), and

the resulting mixture was stirred for 3 h. The reaction solution was applied to a gel filtration column of LH-20, and eluted with methanol. The solvent of fractions containing product was distilled off *in vacuo* and the residue thus obtained was recrystallized from methanol to give glucosyldiflucortolone (deprotected derivative; 111) (408.4 mg). To a portion of the product (102.5 mg) were added, at 0 - 5°C, *p*-chlorobenzoyl chloride (190 μ l) and pyridine (0.9 ml), and, while the reaction temperature was slowly raised to room temperature, the mixture was stirred for 6 h. Then, to the mixture was added methanol (1 ml), and the resulting mixture was stirred at room temperature for 30 min. The reaction solution was applied to a gel filtration column of LH-20, and eluted with methanol. After the solvent of fractions containing product was distilled off *in vacuo*, the residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 4:1) to give 112 as white powder [152.2 mg (yield 42.0%) (109 \rightarrow 112 in two steps)].

10

Compound 111

[0197]

15 $C_{28}H_{38}O_9F_2$ MW = 556.60
 1H -NMR [500MHz, DMSO, Ref = 0.000ppm(TMS)]

20 δ : 3.079 (1H, t, J = 5.49, H-6')
3.118 (1H, t, J = 8.43, H-2)
3.272 (1H, d, J = 7.79, H-3)
3.439 (1H, dd, J = 11.36, H-5)
4.161 (1H, d, J = 8.06, H-1)
6.107 (1H, s, Difluco-4)
6.292 (1H, d, Difluco-1)

25

FAB(+)MS calcd. 556.2; 557(M+H)⁺
MP : 162 - 164°C
IR ν_{max}^{KBr} cm⁻¹ : 1716(C = O position-20), 1630(C=O position-3)

30 Compound 112

[0198]

35 $C_{56}H_{50}O_{13}Cl_4F_2$ MW = 1110.81
 1H -NMR [500MHz, CDCl₃, Ref = 0.000ppm(TMS)]

40 δ : 4.057 (1H, ddd, J = 4.03, H-5)
4.605 (1H, dd, J = 4.03, H-6')
4.693 (1H, dd, J = 12.45, H-6)
5.046 (1H, d, J = 7.70, H-1)
5.471 (1H, dd, J = 9.53, H-2)
5.654 (1H, t, J = 9.86, H-4)
5.843 (1H, t, J = 9.86, H-3)
7.286, 7.349, 7.352, 7.411
(8H, 4d, J = 8.79, ClC₆H₄CO-)
7.762, 7.838, 7.890, 7.902
(8H, 4d, J = 8.79, ClC₆H₄CO-)

45

FAB(+)MS calcd. 1108.2 ; 1109(M+H)⁺
MP : 147 - 149°C
IR ν_{max}^{KBr} cm⁻¹ : 1738(C = O position-20), 1634(C =O position-3)

6) Synthesis of glucosyldiflucortolone (acetyl derivative) 11355 109 \rightarrow 113

[0199] Glucosyldiflucortolone (*p*-toluoyl derivative; 109) (1.55 g) was dissolved in chloroform (50 ml), and to this solution was added, under ice-cooling, 1 M sodium methoxide (1.21 ml). While the reaction temperature was slowly

raised to room temperature, the mixture was stirred for 1 h. Then, to the reaction solution was added methanol (40 ml), and the mixture was stirred at room temperature for 3 h. After the solvent was distilled off *in vacuo*, acetic anhydride (8.0 ml) and pyridine (1.8 ml) were added to the residue under ice-cooling, and the resulting mixture was slowly raised to room temperature, the mixture was stirred for 2 h. To this mixture was further added acetic anhydride (2.6 ml) and 5 pyridine (0.6 ml), the mixture was stirred for 3 h. The reaction solution was poured into ice-water, extracted with chloroform, and the chloroform solution was washed successively with saturated sodium bicarbonate solution, 5% copper sulfate solution, and saturated sodium chloride solution. The chloroform solution was dried over anhydrous magnesium sulfate, and then the solvent was evaporated *in vacuo*. The residue thus obtained was recrystallized from ethyl acetate to give 113 as white powder [668 mg (yield 61.2%)].

10

Compound 113

[0200]

15 $C_{36}H_{46}O_{13}F_2$ MW = 724.75
 1H -NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

18 δ : 2.117, 2.069, 2.051, 2.019 (12H, 4s, CH_3COO-)
3.663 (1H, ddd, J = 5.13, H-5)
20 4.198 (1H, dd, J = 2.93, H-6)
4.389 (1H, dd, J = 12.46, H-6)
4.733 (1H, d, J = 8.06, H-1)
5.005 (1H, dd, J = 9.52, H-2)
25 5.007 (1H, t, J = 9.52, H-4)
5.235 (1H, t, J = 9.52, H-3)
6.383 (1H, d, Difluco-1)
6.429 (1H, s, Difluco-4)

30 FAB(+)MS calcd. 724.3 ; 725($M+H$)⁺
MP : 233 - 235°C
IR ν_{max}^{KBr} cm^{-1} 1760(C = O position-20), 1671(C = O position-3)

Example 24

35 Synthesis of glucosyldexamethasone (acetyl derivative) (Fig. 24)

1) Glucosyldexamethasone (acetyl derivative) 5 β \rightarrow 114 β

40 [0201] A deprotected derivative (5 β) of glucosyldexamethasone (β -anomer) (278 mg) was dissolved in acetic anhydride (1.75 ml), and to this solution was added, under ice-cooling, pyridine (0.40 ml). While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 1 h. The reaction solution was poured into ice-water, and extracted with chloroform. The chloroform solution was washed successively with saturated sodium bicarbonate solution, 5% copper sulfate solution, and saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by 45 silica gel column chromatography (hexane:ethyl acetate = 1:2) to give white powder (198 mg). This product was further purified by HPLC using a reversed phase partition column (acetonitrile-water) to give 114 β as white powder [147 mg (yield 40.5%)].

50

Compound 114 β

55

$C_{36}H_{47}O_{14}F$ MW = 722.76
 1H -NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

58 δ : 2.119, 2.094, 2.047, 2.022 (12H, 4s, CH_3COO-)
3.690 - 3.654 (1H, m, H-5)
4.219 (1H, dd, J = 12.09, 3.29, H-6)

4.336 (1H, dd, J = 4.77, H-6')
 4.746 (1H, d, J = 8.06, H-1)
 5.027 (1H, dd, J = 9.15, H-2)
 5.087 (1H, t, H-4)
 5.245 (1H, t, H-3)
 6.121 (1H, s, Dex-4)
 6.347 (1H, d, Dex-1)

5
 10 FAB(+)MS calcd. 722.29 ; 723(M+H)⁺, 705(M-H₂O)⁺
 MP : 125 - 128°C
 IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹ 1758(C = O position-20), 1666(C = O position-3)

Example 25

15 Synthesis of galactosyldexamethasone (acetyl derivative) (Fig. 25)

1) Synthesis of galactosyldexamethasone (acetyl derivative) 115 β 14 β \rightarrow 115 β

20 [0203] Galactosyldexamethasone (*p*-toluoyl derivative; 14 β) (762 mg) was dissolved in chloroform (25 ml), and to this solution was added, under ice-cooling, 1 M sodium methoxide (592 μ l). While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 2 h. To this reaction solution was added methanol (25 ml), and the mixture was stirred at room temperature for 1 h. After the solvent was evaporated *in vacuo*, acetic anhydride (3.90 ml) and pyridine (0.90 ml) were added to the residue under ice-cooling. While the reaction temperature was raised slowly to room temperature, the mixture was stirred for 12 h. To this mixture were further added acetic anhydride (1.30 ml) and pyridine (0.30 ml), and the resulting mixture was stirred at room temperature for 4 h. The reaction solution was poured onto ice-water, and extracted with chloroform. The chloroform solution was washed successively with saturated sodium bicarbonate solution, 5% copper sulfate solution and saturated sodium chloride solution. After the solvent was distilled off *in vacuo*, the residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 2:3) to give white powder (462 mg). This product was further purified by HPLC using a reversed phase partition column (acetonitrile-water) to give 115 β as white powder [171 mg (yield 31.9%)].

Compound 115 β

[0204]

35 $\text{C}_{36}\text{H}_{47}\text{O}_{14}\text{F}$ MW = 722.76
 1H-NMR [500MHz, CDCl₃, Ref = 0.000ppm(TMS)]

40 δ : 2.190, 2.132, 2.101, 2.002 (12H, 4s, $\text{CH}_2\text{COO}-$)
 4.454 (1H, dd, H-6')
 4.575 (1H, d, J = 8.06, H-1)
 4.621 (1H, dd, H-2)
 5.032 (1H, t, H-3)
 5.239 (1H, t, H-2)
 5.392 (1H, d, H-4)
 6.115 (1H, s, Dex-4)
 6.331 (1H, d, Dex-1)

50 FAB(+)MS calcd. 722.29 ; 723(M+H)⁺, 705(M-H₂O)⁺
 MP : 138 - 141°C
 IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹ 1753(C = O position-20), 1666(C = O position-3)

55

Example 26

Synthesis of glucosylbetamethasone valerate (*m*-toluoyl derivative) (Fig. 26)

5 1) Synthesis of glucosylbetamethasone valerate (*m*-toluoyl derivative) 117

96+116 → 117

[0205] Betamethasone valerate (116) (405 mg) was dissolved in acetonitrile (23 ml), and to this solution were 10 added molecular sieve 3A (460 mg) and silver triflate (437 mg). To this mixture was added, under an argon atmosphere and at 0 - 5°C, a glucose bromide (*m*-toluoyl derivative (96) (1.22 g). While the reaction temperature was raised slowly to room temperature, the mixture was stirred for 5 h. After the reaction solution was filtered, the solvent of the mother liquor was evaporated *in vacuo*. The residue was dissolved in chloroform, and washed with saturated sodium chloride solution. After the solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 5:4) to give white powder 15 (779 mg). This product was further purified by HPLC using a reversed phase partition column (acetonitrile-water) to give β -anomer (117 β) [407 mg (yield 43.1%)] and α -anomer (117 α) [59 mg (yield 6.3%)], respectively, both as white powder.

Compound 117 β

20

[0206]

$C_{65}H_{71}O_{15}F$ MW = 1111.2
 1H -NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

25

δ : 2.352, 2.307, 2.290, 2.277 (12H, 4s, $CH_2C_6H_4O^-$)
4.088-4.051 (1H, m, H-5)
4.353 (1H, d, J = 9.16, H-6)
4.663 (1H, d, J = 4.76, H-6')
5.135 (1H, d, J = 8.06, H-1)
5.481 (1H, dd, H-2)
5.675 (1H, t, H-4)
5.869 (1H, t, H-3)
6.181 (1H, s, Bet-4)
6.400 (1H, d, Bet-1)
7.800, 7.712, 7.475 (8H, 3d, J = 7.69, $CH_3C_6H_4O^-$)

30

FAB(+)MS calcd. 1110.48 ; 1111(M+H) $^+$,
1094(M-H₂O) $^+$
40 MP : 113 - 115°C
IR ν_{max}^{KBr} cm⁻¹ 1734(C = O position-20), 1668(C = O position-3)

Compound 117 α

45 [0207]

$C_{65}H_{71}O_{15}F$ MW = 1111.2
 1H -NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

50

δ : 2.386, 2.339, 2.333, 2.284 (12H, 4s, $CH_2C_6H_4O^-$)
4.088-4.051 (1H, m, H-5)
5.330 (1H, d, J = 3.67, H-1)
6.162 (1H, s, Bet-4)
6.385 (1H, d, Bet-1)
7.831, 7.772, 7.676 (8H, 3d, J = 8.06, $CH_3C_6H_4O^-$)

55

FAB(+)MS calcd. 1110.48 ; 1111(M+H) $^+$,
1094(M-H₂O) $^+$

MP : 105 - 108°C

IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} 1732(C = O position-20), 1668(C = O position-3)Synthesis of β -rhamnosyldexamethasone (Fig. 27)

5

1) Synthesis of a protected (acetyl) derivative of rhamnosyldexamethasone 119 (glucosylation)

[0208] Dexamethasone (6) (1.10 g) and rhamnose (o-acetyl, S-methyl derivative) 118 (1.12 g) were dissolved in tetrahydrofuran (10 ml), and this solution was added to molecular sieve 4A (1.2 g) contained in a brown reaction vessel. To this mixture was added, at -10°C, methyl triflate (2 ml), and, while the reaction temperature was slowly raised to room temperature, the mixture was stirred for 4 h. The reaction solution was diluted with ethyl acetate (10 ml) and neutralized by the addition of triethylamine. The mixture was filtered, diluted with ethyl acetate (300 ml), and washed with saturated sodium bicarbonate solution followed by saturated sodium chloride solution. After the solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (toluene:acetone = 1:1) to give 119 β as white powder [312.5 mg (yield 16.8%)].

Compound 119 β

[0209]

20

 $\text{C}_{34}\text{H}_{45}\text{FO}_{12}$ MW = 664.72Rf = 0.62 (silica gel TLC, CHCl_3 : methanol = 20 : 1) $^1\text{H-NMR}$ [500MHz, CDCl_3 , Ref = 0.000ppm(TMS)]

25

δ : 7.213 (1H, d, Dexta-H-2, $J_{2,1}$ = 10.3)
 6.336 (1H, dd, Dexta-H-1, $J_{1,4}$ = 1.5)
 6.115 (1H, d, Dexta-H-4)
 5.376 (1H, dd, H-2, $J_{2,3}$ = 3.3, $J_{2,1}$ = 1.8)

30

5.321 (1H, dd, H-3, $J_{3,4}$ = 9.9)5.088 (1H, dd, H-4, $J_{4,5}$ = 9.9)

4.785 (1H, d, H-1)

4.511 (1H, d, Dexta-H-21, J_{gem} = 16.5)

4.418 (1H, d, Dexta-H-21')

4.380 (1H, m, Dexta-H-11)

35

4.014 (1H, dq, H-5, $J_{5,6}$ = 6.2)

3.118 (1H, m, Dexta-H-16)

2.617 (1H, m, Dexta-H-6)

2.157, 2.057, 2.003 (3H x 3, each s, OAc x 3)

1.548 (3H, s, Dexta-H-19)

40

1.218 (3H, d, H-7')

1.055 (3H, s, Dexta-H-18)

0.910 (3H, d, Dexta-16CH₃, $J_{16\text{CH}_3,16}$ = 7.3)FAB(+)MS ; 665(M+H)⁺

MP : 137 - 139°C

IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} 3430(O-H), 1752(C = O), 1668(C = O)2) Synthesis of a deprotected derivative of rhamnosyldexamethasone (synthesis of 119 β →120 β)

50

[0210] A protected derivative of rhamnosyldexamethasone (119 β) (103.4 mg) was dissolved in methanol (1 ml), and to this solution was added 1 M sodium methoxide (40 μ l). The mixture was stirred at room temperature for 1 h. The reaction solution was applied to a gel filtration column of LH-20, and eluted with methanol. The solvent of fractions containing product was distilled off *in vacuo* to give 120 β as white powder [55.4 mg (yield 64%)].

55

Compound 120 β

[0211]

5 $C_{28}H_{39}FO_9$ MW = 538.61
 Rf = 0.67(silica gel TLC, $CHCl_3$: methanol = 1 : 1)
 1H -NMR [500MHz, CD_3OD , Ref = 0.000ppm(TMS)]

8 : 7.403 (1H, d, Dexa-H-2, $J_{2,1}$ = 10.3)
 10 6.286 (1H, dd, Dexa-H-1, $J_{1,4}$ = 1.8)
 11 6.115 (1H, d, Dexa-H-4)
 12 4.682 (1H, d, H-1, $J_{1,2}$ = 1.5)
 13 4.649 (1H, d, Dexa-H-21, J_{gem} = 18.3)
 14 4.412 (1H, d, Dexa-H-21')
 15 4.259 (1H, m, Dexa-H-11)
 16 3.951 (1H, dd, H-2, $J_{2,3}$ = 3.3)
 17 3.698 (1H, dd, H-3, $J_{3,4}$ = 9.5)
 18 3.596 (1H, dq, H-5, $J_{5,4}$ = 9.5, $J_{5,6}$ = 6.2)
 19 3.383 (1H, dd, H-4)
 20 3.062 (1H, m, Dexa-H-16)
 21 2.713 (1H, m, Dexa-H-6)
 22 2.480 (1H, m, Dexa-H-6')
 23 2.317 (1H, m, Dexa-H-12)
 24 2.222 (1H, m, Dexa-H-14)
 25 1.876 (1H, m, Dexa-H-7)
 26 1.727 (1H, m, Dexa-H-15)
 27 1.580 (3H, s, Dexa-H-19)
 28 1.265 (3H, d, H-6)
 29 1.002 (3H, s, Dexa-H-18)
 30 0.855 (3H, d, Dexa-16 CH_3 , $J_{16CH_3,16}$ = 6.9)

FAB(+)MS ; 539($M+H$)⁺
 MP : 144 - 146°C (decomp.)
 IR ν_{max}^{KBr} cm^{-1} 3418(O-H), 1719(C = O), 1663(C = O)

35 **Claims**1. **Glycosides of steroid compounds as the aglycon, wherein:**

40 the 21-position of said steroid compounds is substituted with simple sugars or acylated derivatives of said simple sugars,

the hydroxyl groups of said simple sugars or said acylated simple sugars are protected with toluoyl, benzoyl, p-chlorobenzoyl, or arylalkyl groups, and

45 said steroid compounds consist of dexamethasone, betamethasone, the dideacyl derivative of diflupredonate, diflurasone, diflucortolone or betamethasone valerate.

2. **Compounds as defined in claim 1, for use as an anti-inflammatory agent.**50 **3. Glycosides of anti-inflammatory steroid compounds as the aglycon for use as an anti-inflammatory agent, wherein:**

the 21-position of said steroid compounds is substituted with simple sugars or acylated derivatives of said simple sugars, and

55 the hydroxyl groups of said simple sugars or said acylated simple sugars are protected with toluoyl, benzoyl, p-chlorobenzoyl, or arylalkyl groups.

Patentansprüche

1. Glykoside von Steroidverbindungen als dem Aglykon, wobei:

5 die 21-Stellung der Steroidverbindungen mit einfachen Zuckern oder acylierten Derivaten der einfachen Zucker substituiert ist,
10 die Hydroxylgruppen der einfachen Zucker oder der acylierten einfachen Zucker mit Toluoyl-, Benzoyl-, p-Chlorbenzoyl- oder Arylalkylgruppen geschützt sind, und
15 die Steroidverbindungen aus Dexamethason, Betamethason den Didesacylderivaten von Diflupredonat, Diflurason, Diflucortolon oder Betamethasonvalerat bestehen.

2. Verbindungen nach Anspruch 1 zur Verwendung als entzündungshemmendes Mittel.

15 **3. Glykoside von entzündungshemmenden Steroidverbindungen als dem Aglykon zur Verwendung als entzündungshemmende, Mittel, wobei:**
20 die 21-Stellung der Steroidverbindungen mit einfachen Zuckern oder acylierten Derivaten der einfachen Zucker substituiert ist, und
25 die Hydroxylgruppen der einfachen Zucker oder der acylierten einfachen Zucker mit Toluoyl-, Benzoyl-, p-Chlorbenzoyl- oder Arylalkylgruppen geschützt sind.

25 Revendications

1. Glycosides de composés stéroïdes de type aglycone, dans lesquels :

30 la position 21 desdits composés stéroïdes est substituée par des sucres simples ou des dérivés acylés desdits sucres simples,
les groupes hydroxyle desdits sucres simples ou desdits sucres simples acylés sont protégés par des groupes toluoyle, benzoyle, p-chlorobenzoyle ou arylalkyle, et
lesdits composés stéroïdes consistent en la dexaméthasone, la bétaméthasone, le dérivé didésacyle du difluprédonate, la diflurasone, la diflucortolone ou le valérate de bétaméthasone

35 2. Composés tels que définis dans la revendication 1, pour utilisation comme agent anti-inflammatoire.

3. Glycosides de composés stéroïdes anti-inflammatoires de type aglycone pour utilisation comme agent anti-inflammatoire dans lesquels :

40 la position 21 desdits composés stéroïdes est substituée par des sucres simples ou des dérivés acylés desdits sucres simples, et
les groupes hydroxyle desdits sucres simples ou desdits sucres simples acylés sont protégés par des groupes toluoyle, benzoyle, p-chlorobenzoyle ou arylalkyle.

45

50

55

Fig. 1

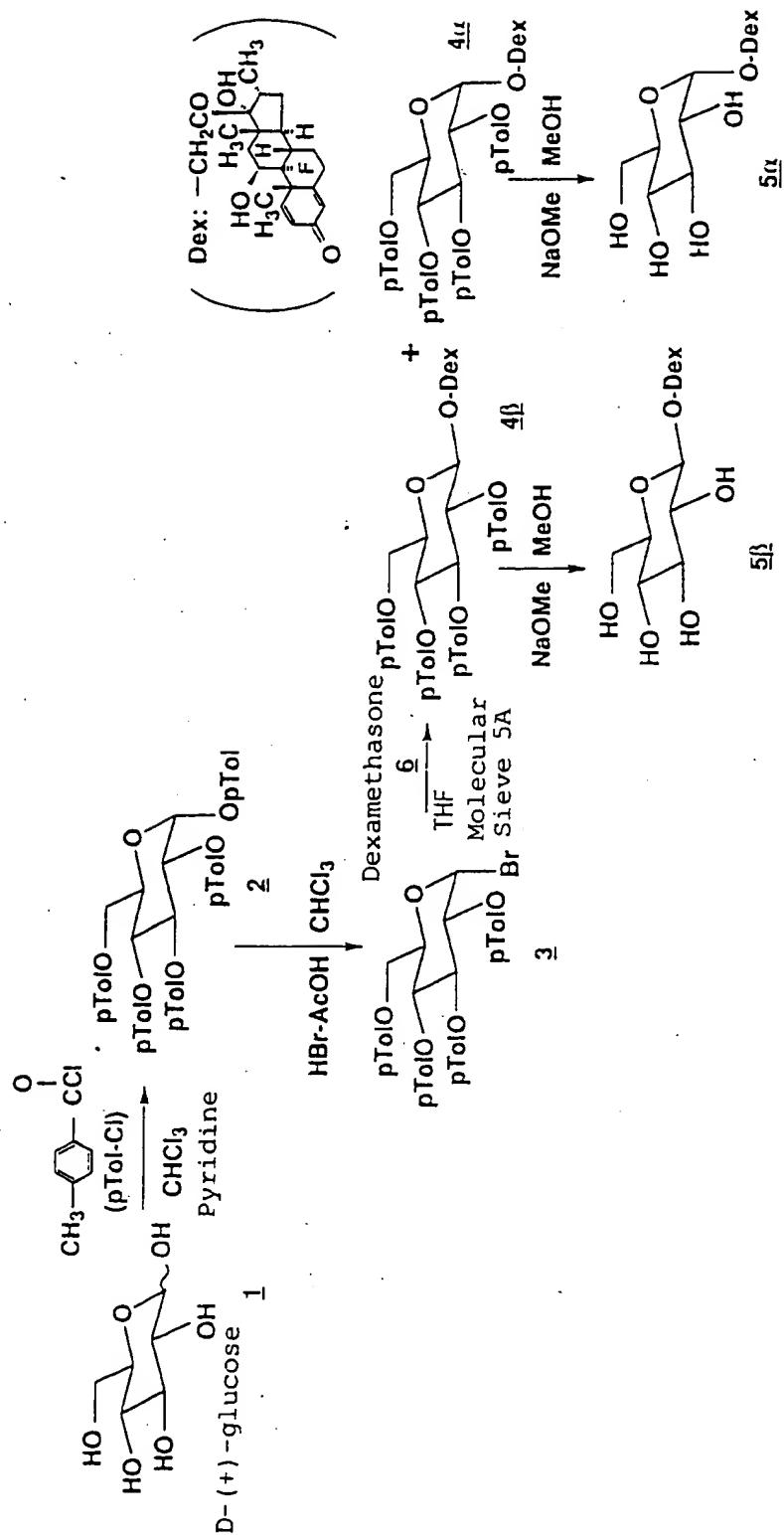


Fig. 2

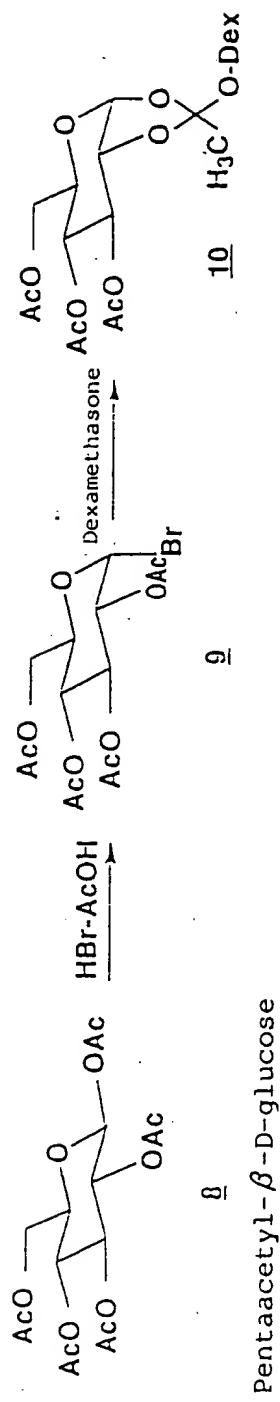
Pentaacetyl- β -D-glucose

Fig. 3

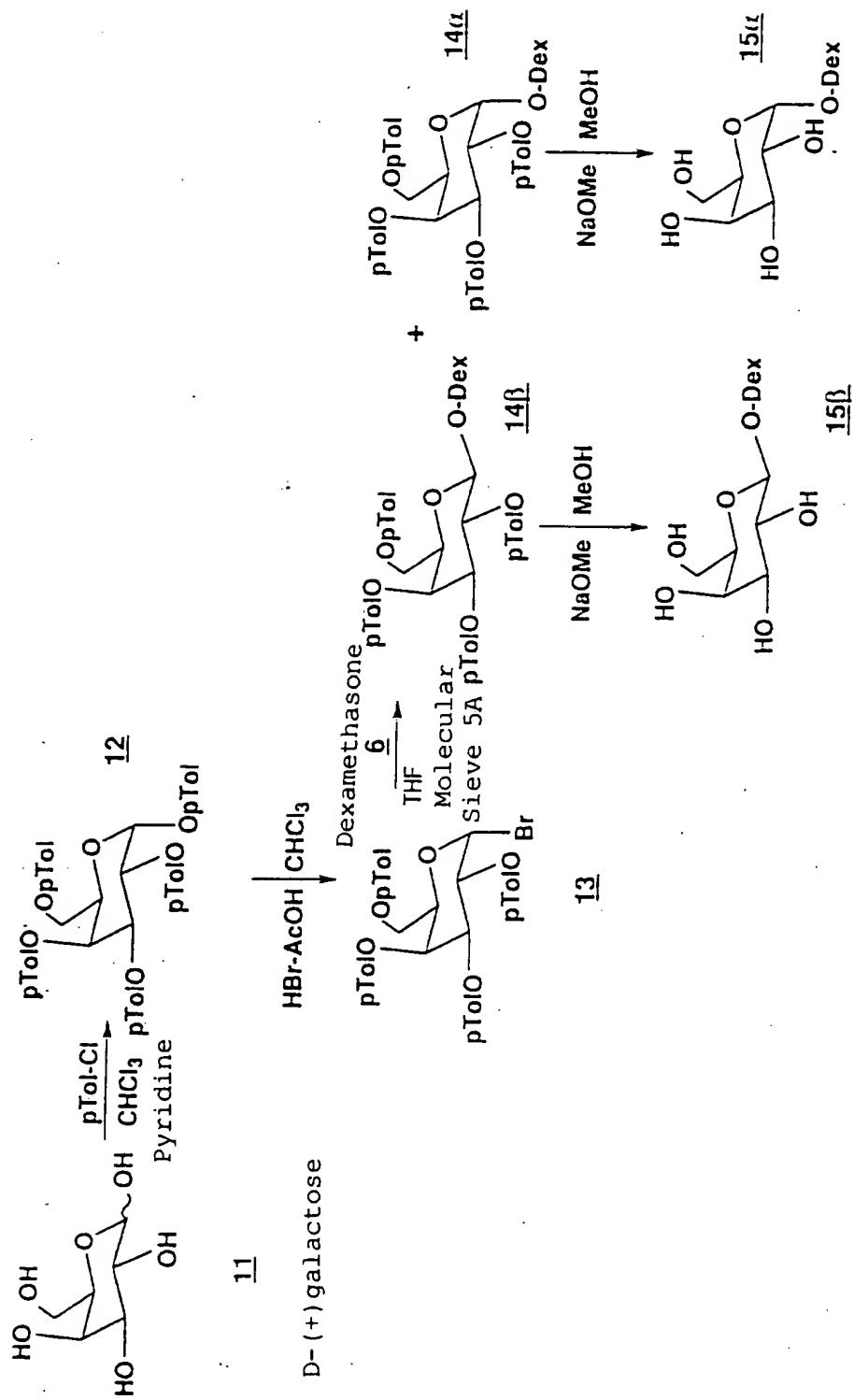


Fig. 1

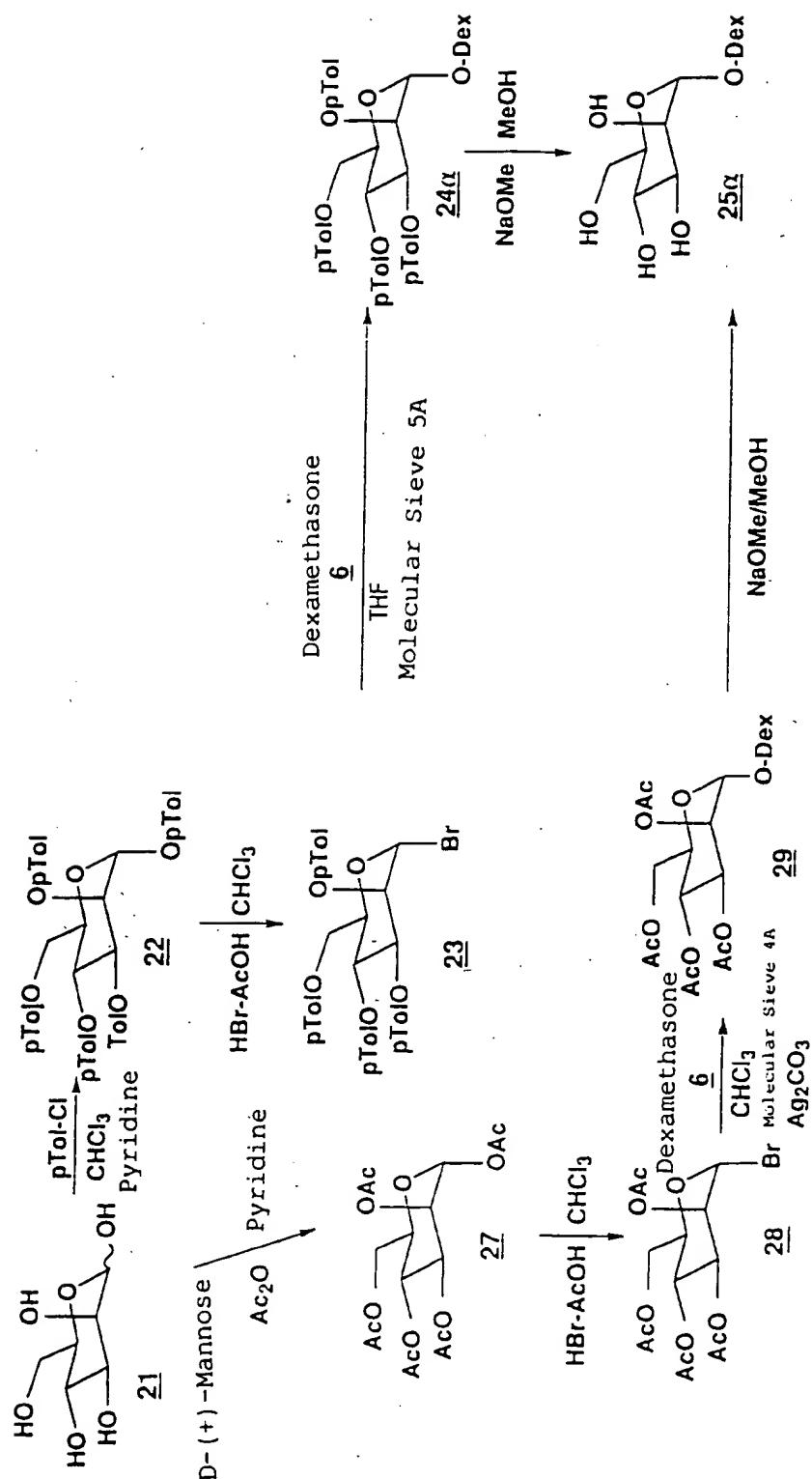


Fig. 5

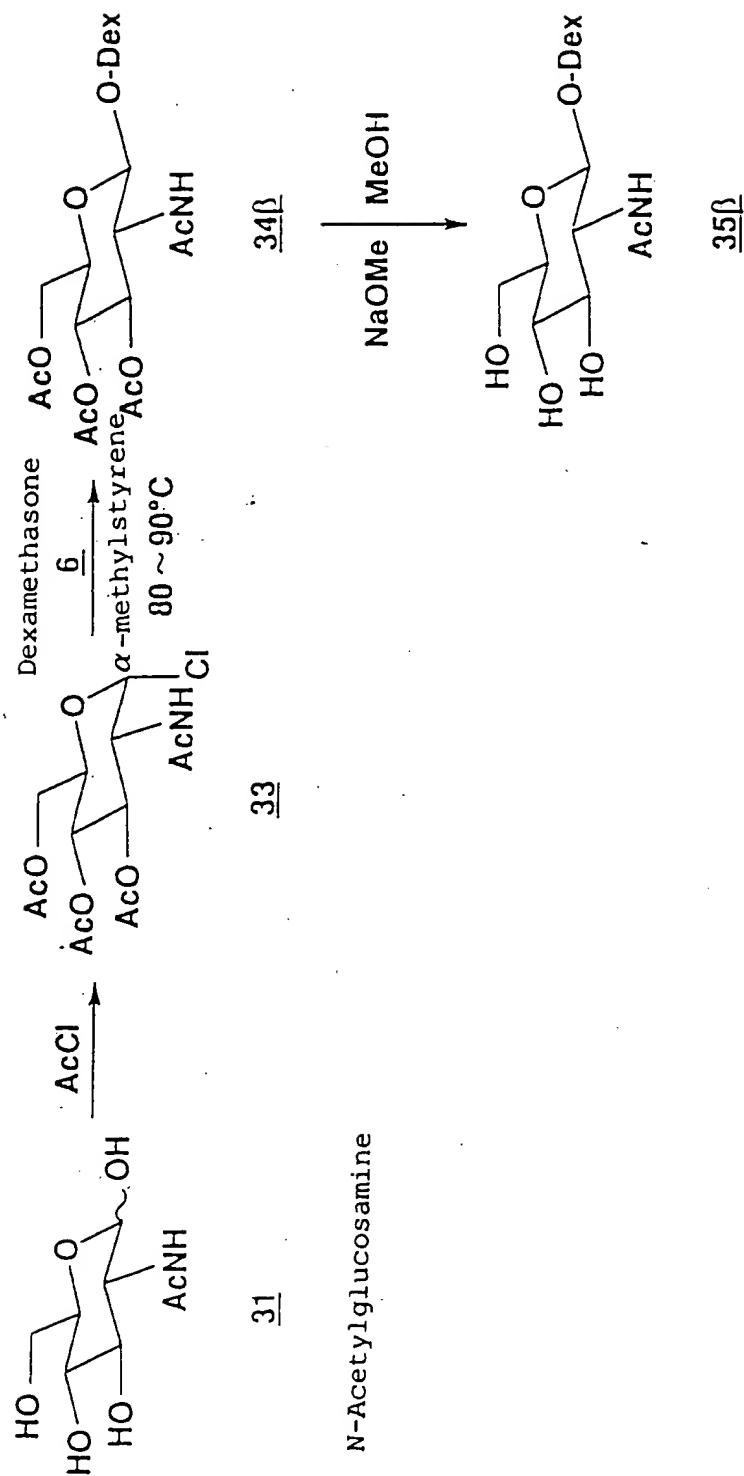


Fig. 6

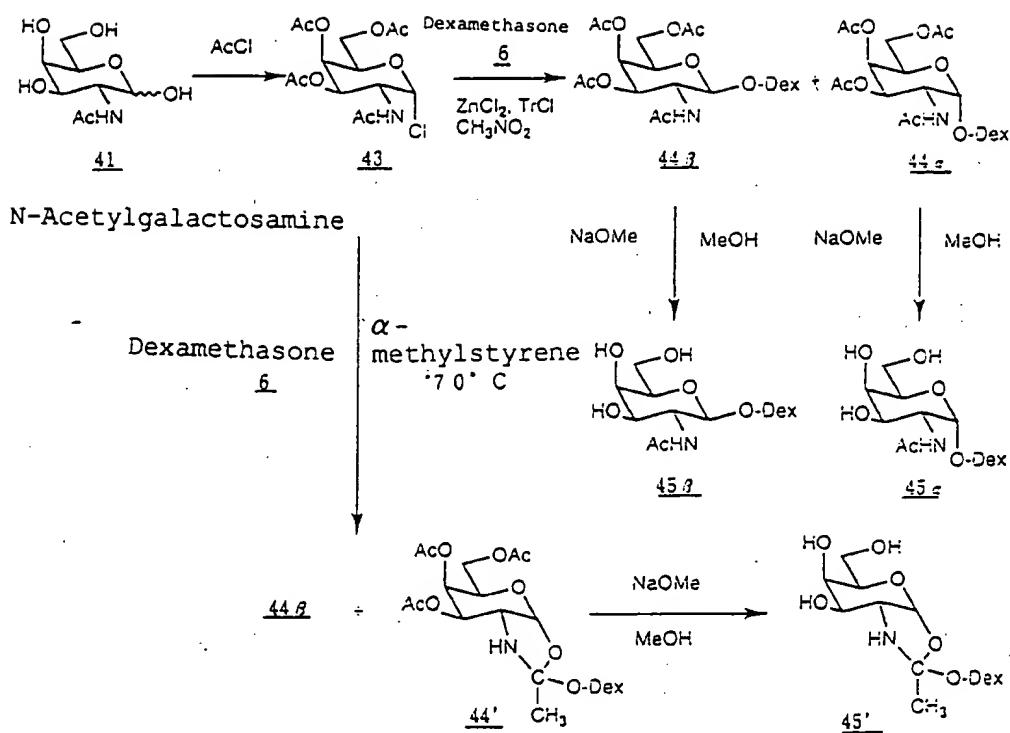


Fig. 7

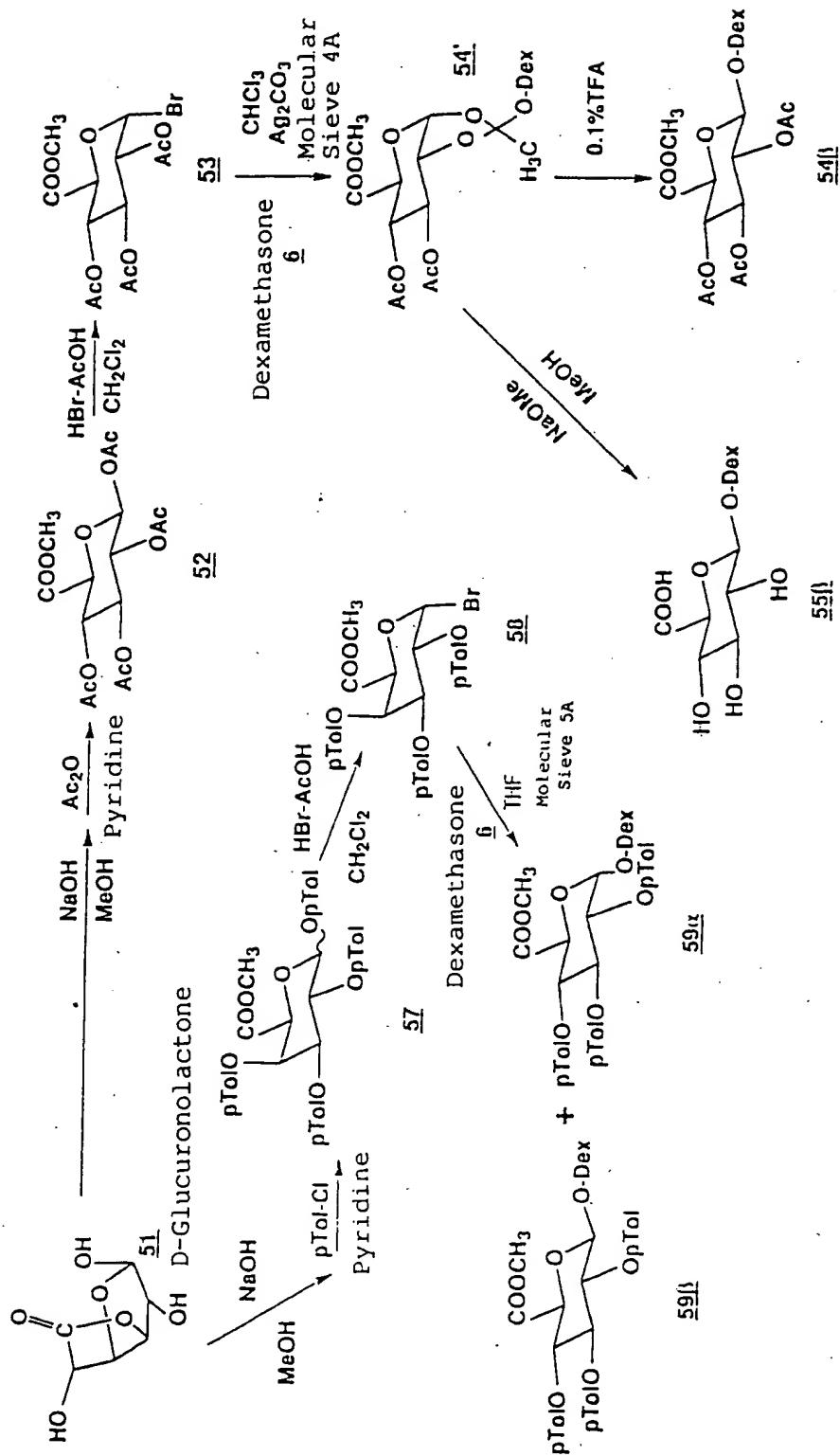


Fig. 8

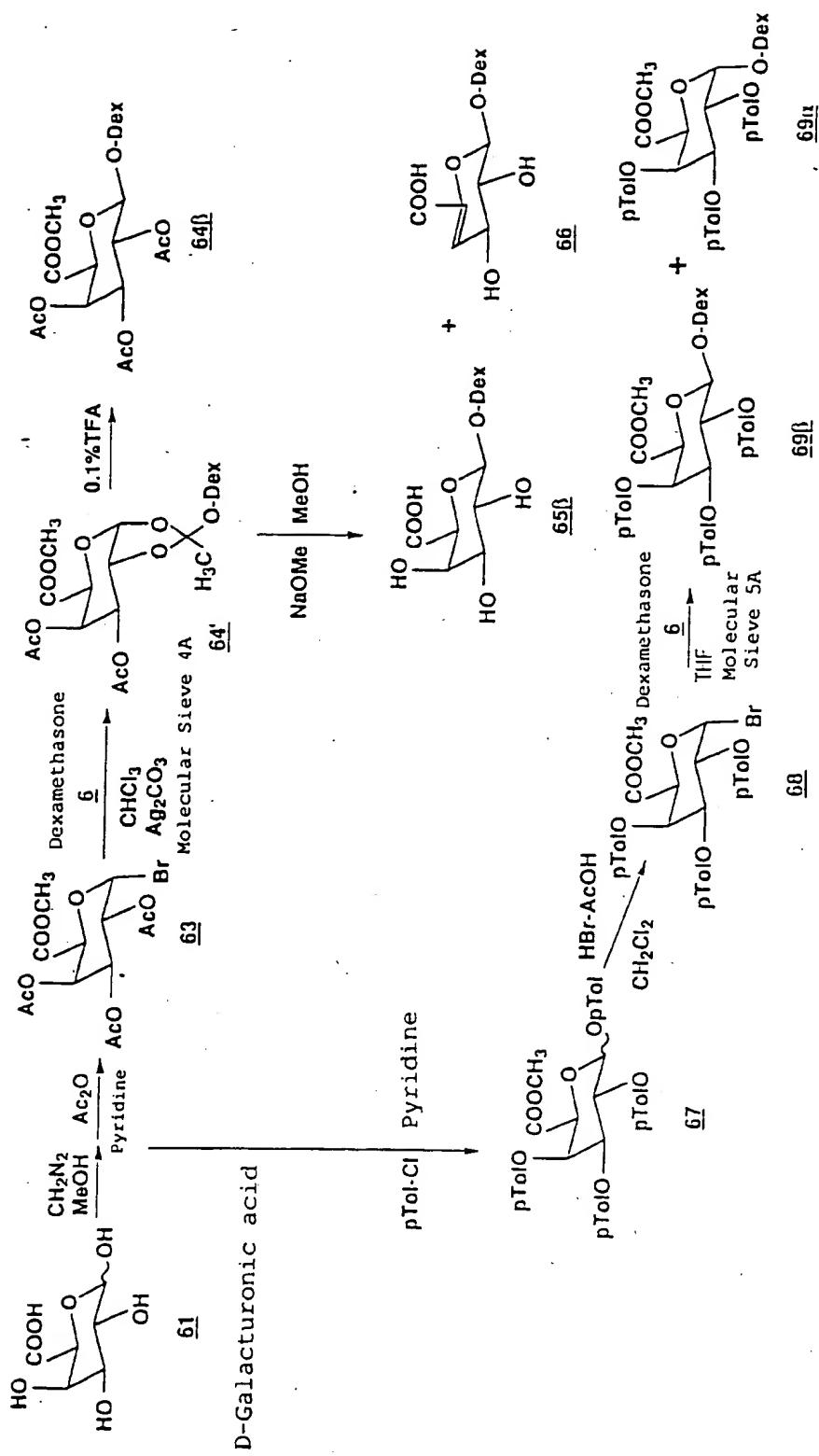


Fig. 9

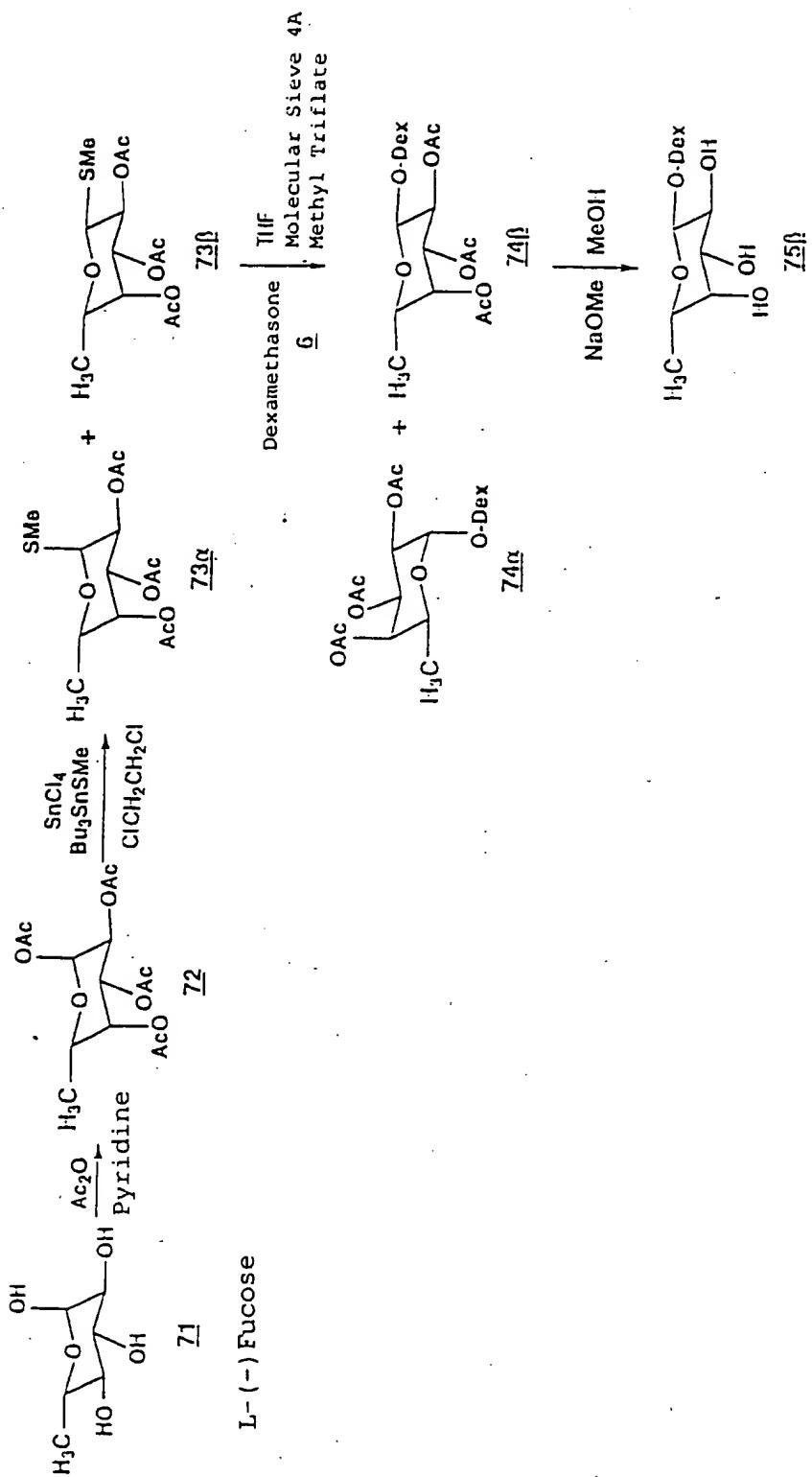


Fig. 10

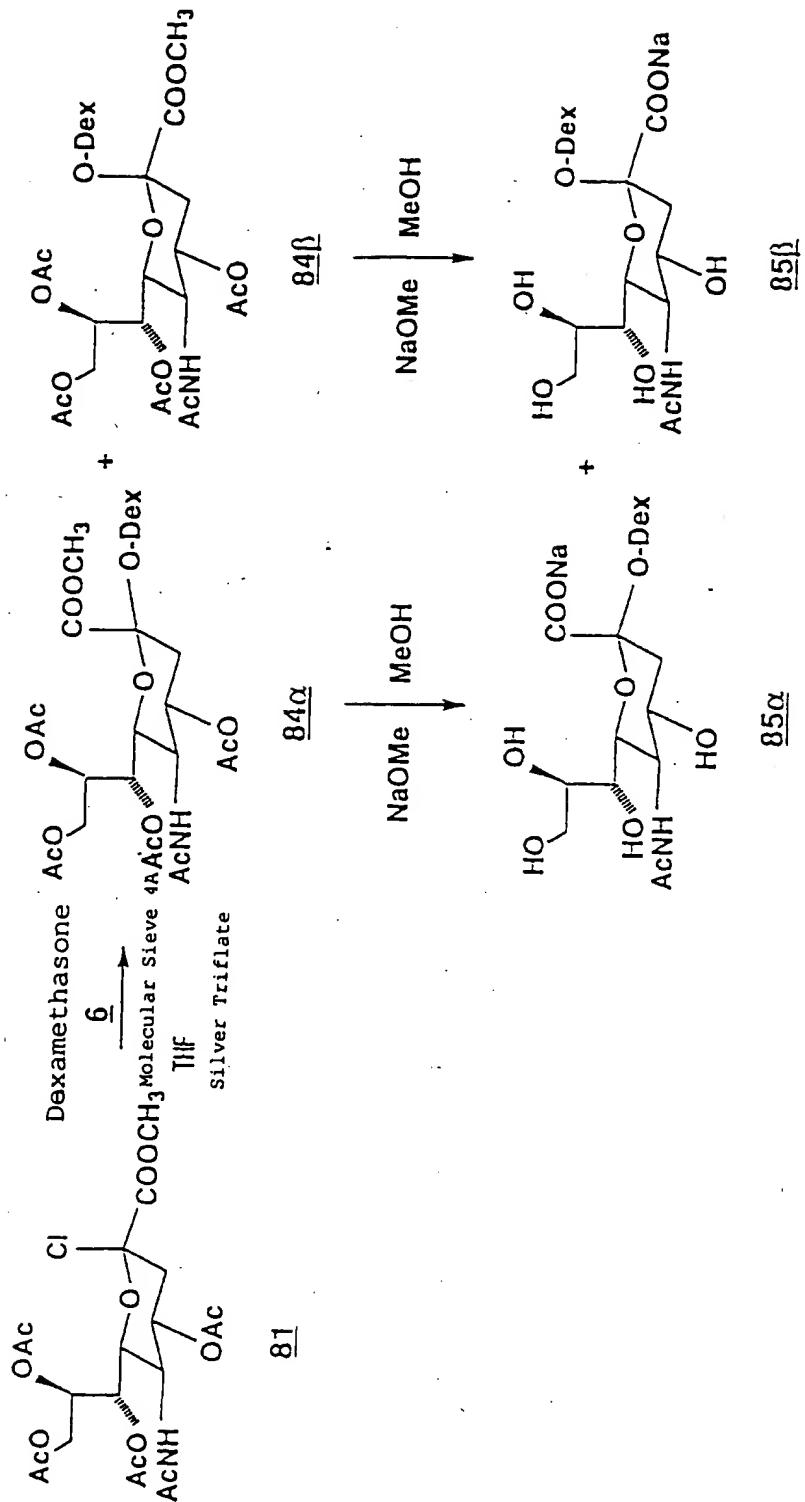


Fig. 1 1

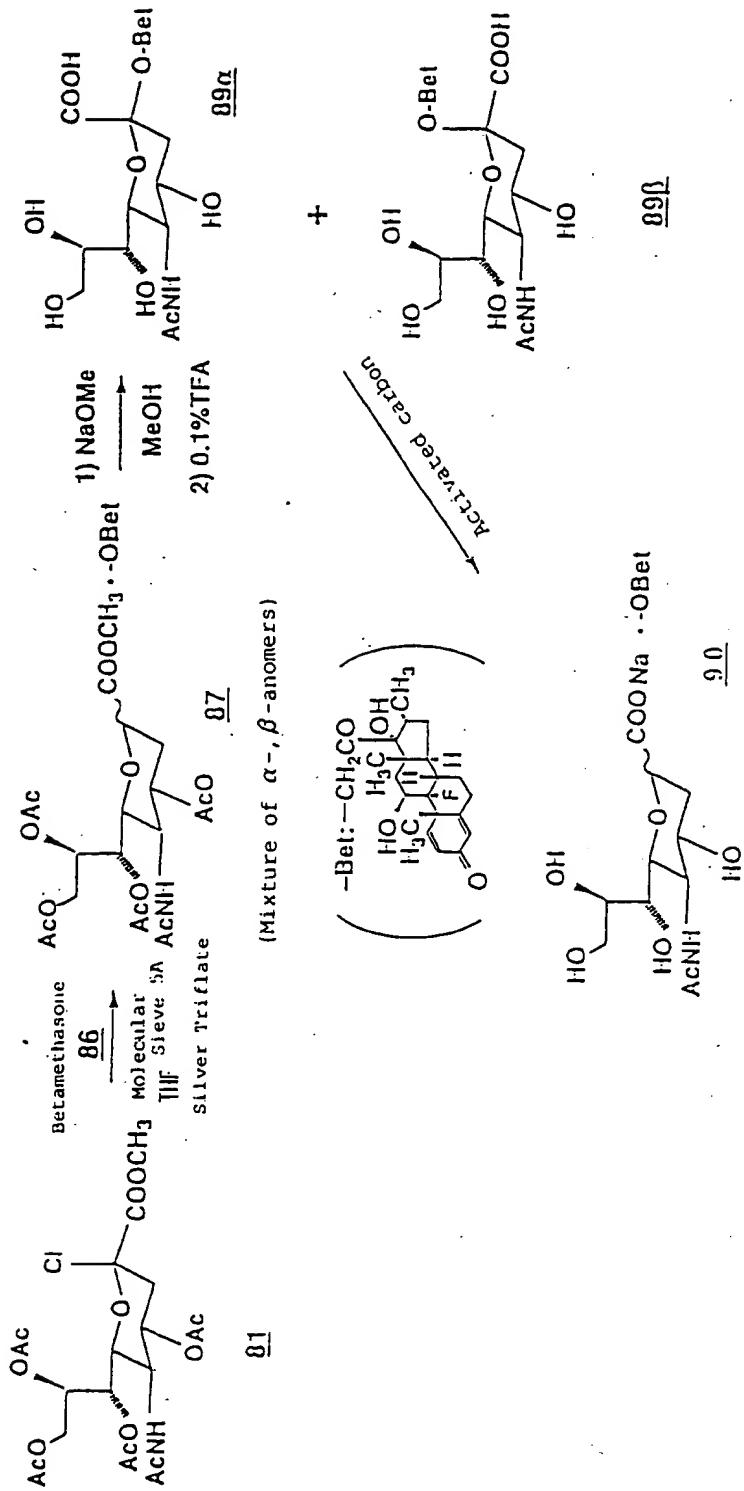


Fig. 1 2

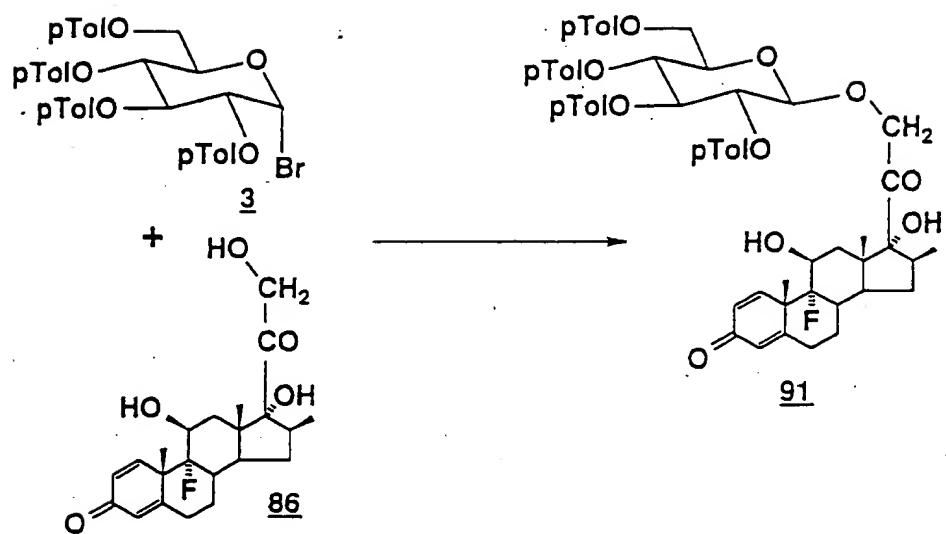


Fig. 1 3

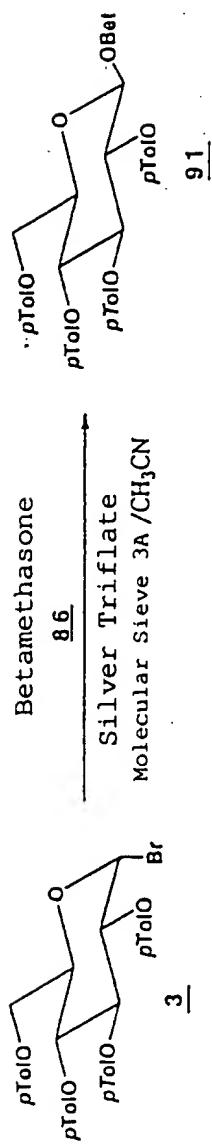


Fig. 1 4

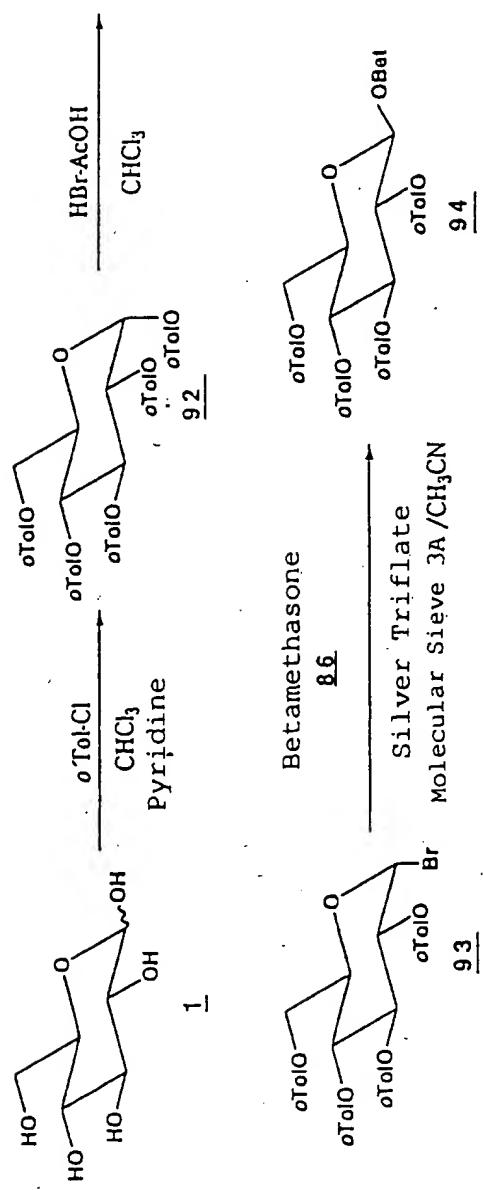


Fig. 1 5

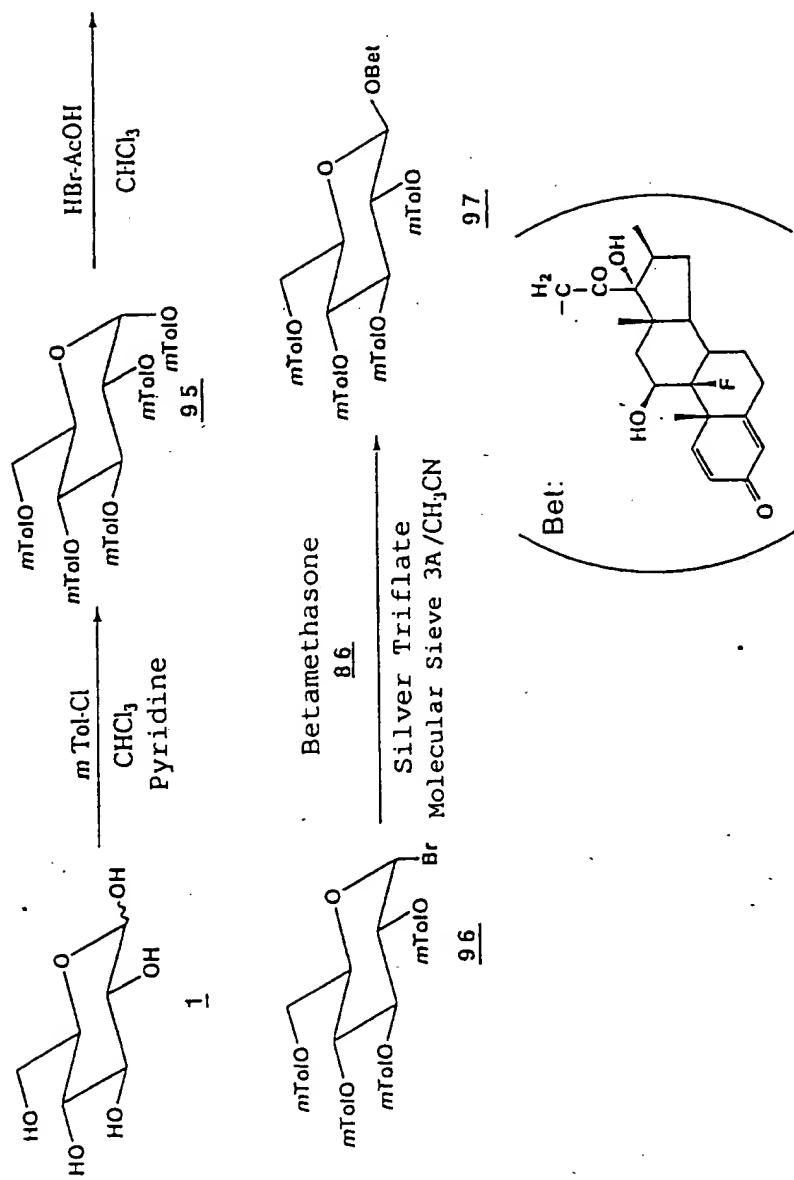


Fig. 16

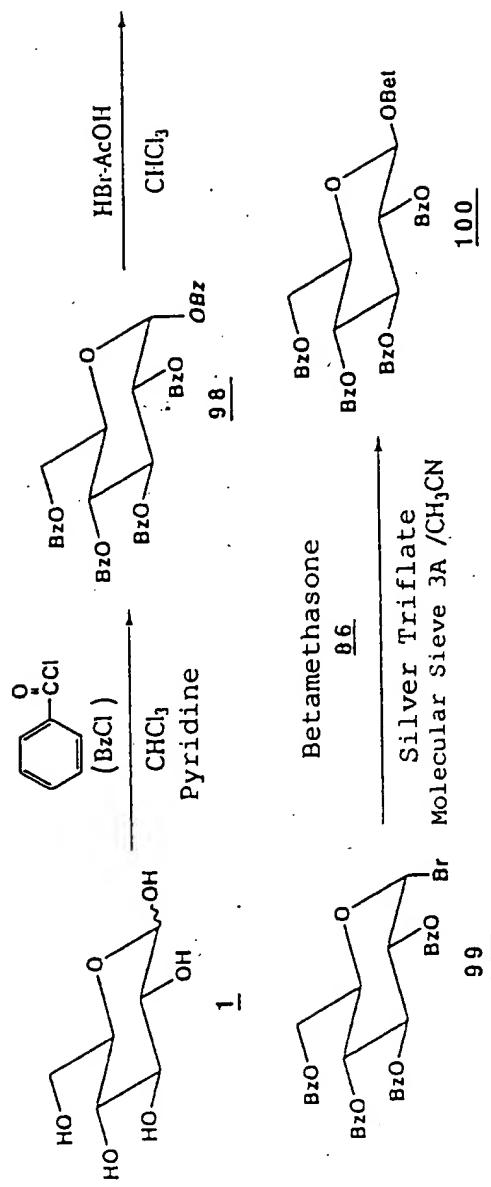


Fig. 1 7

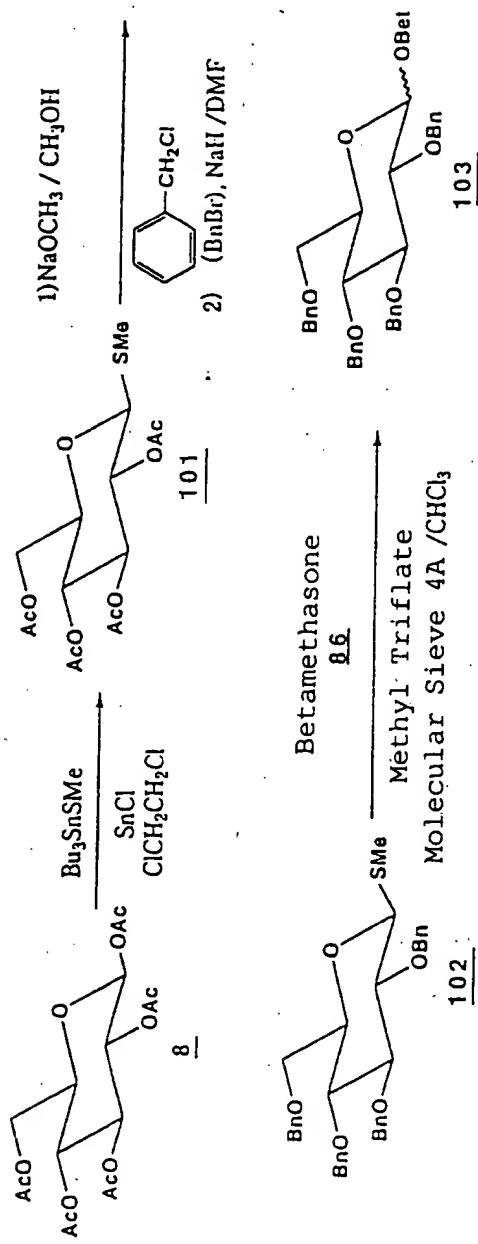


Fig. 1 3

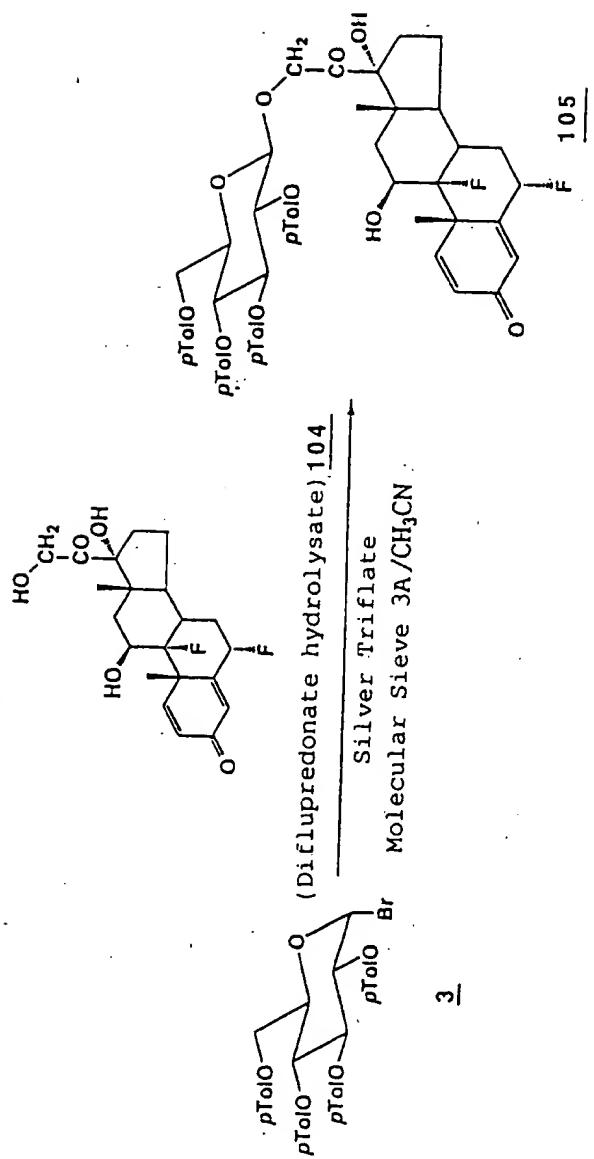


Fig. 1 9

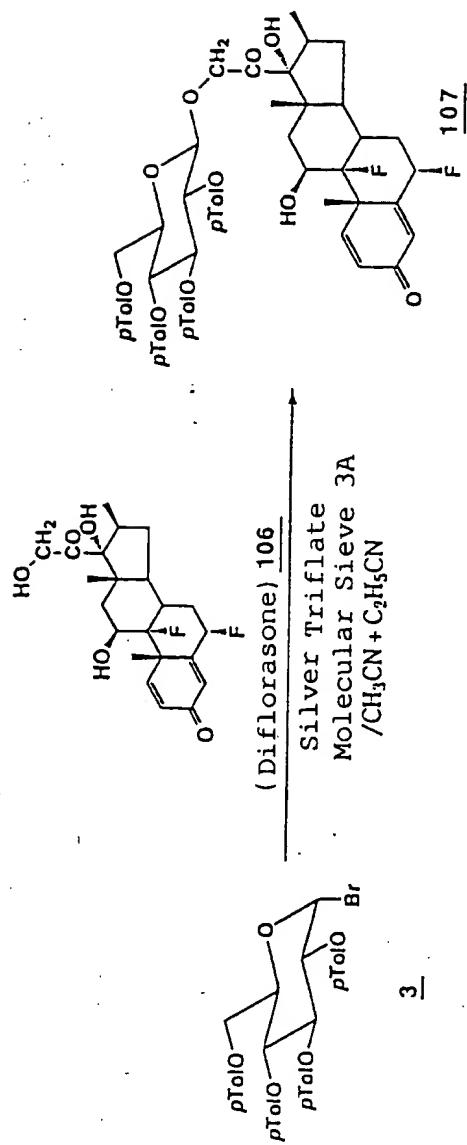


Fig. 20

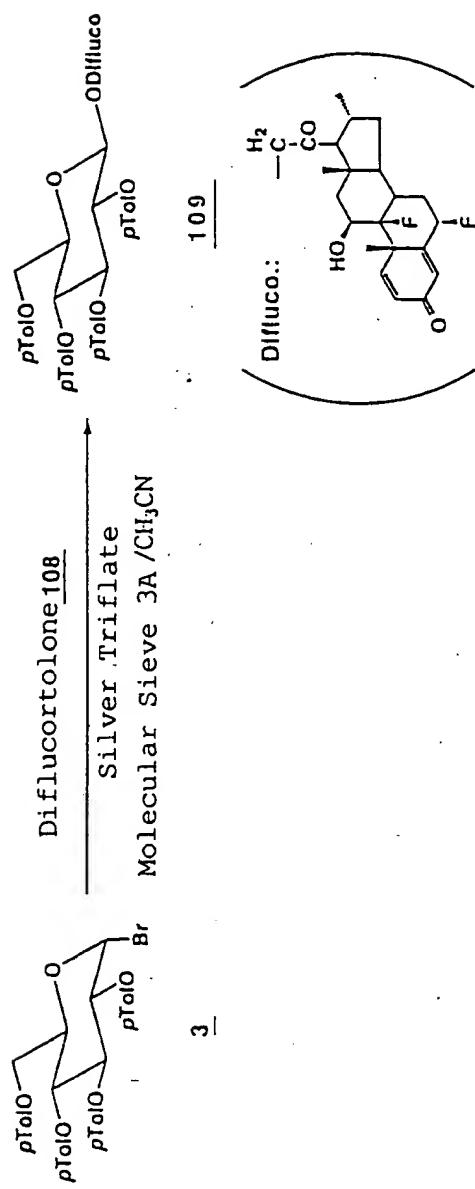


Fig. 2 1

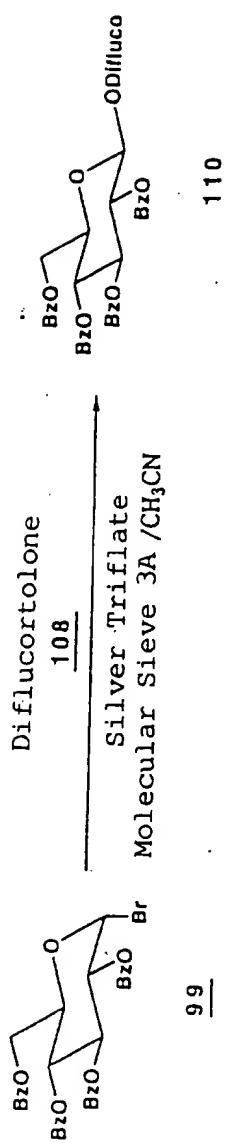


Fig. 2 2

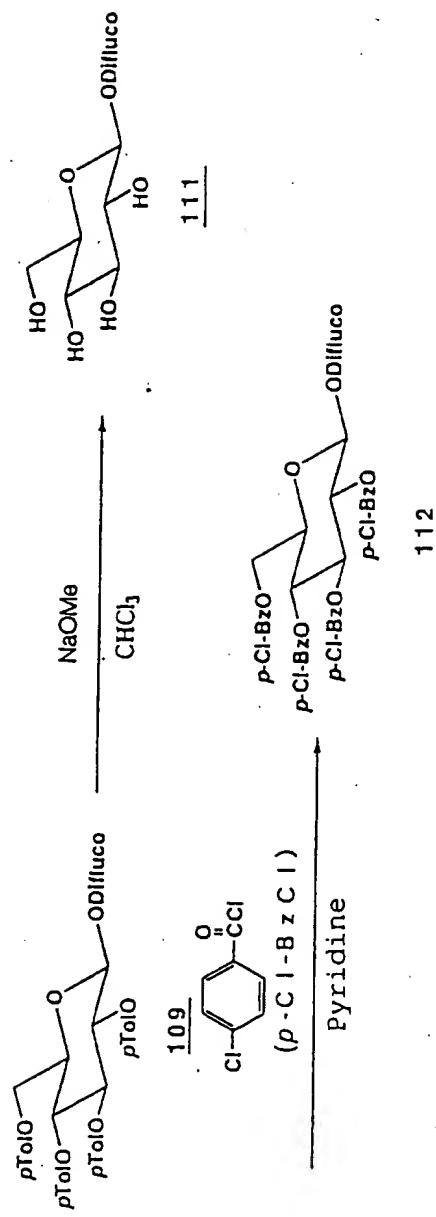


Fig. 2 3

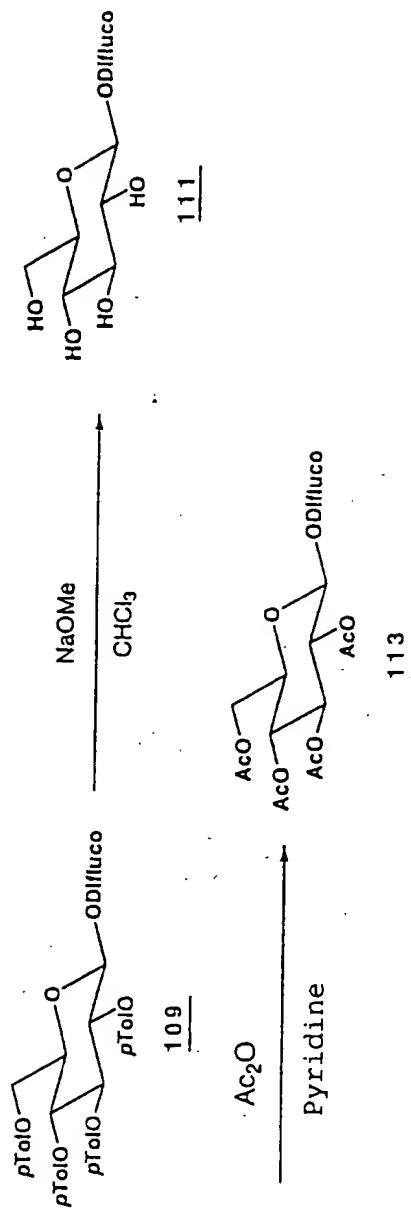


Fig. 24

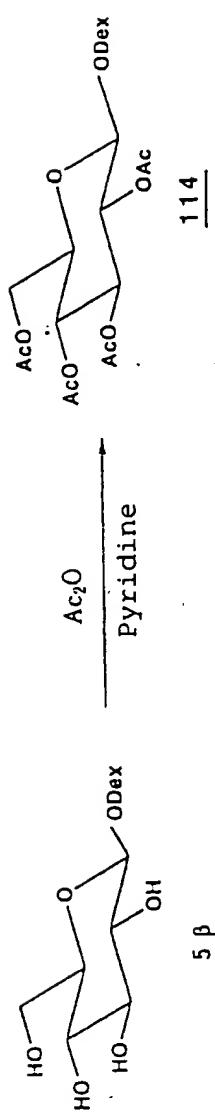


Fig. 25

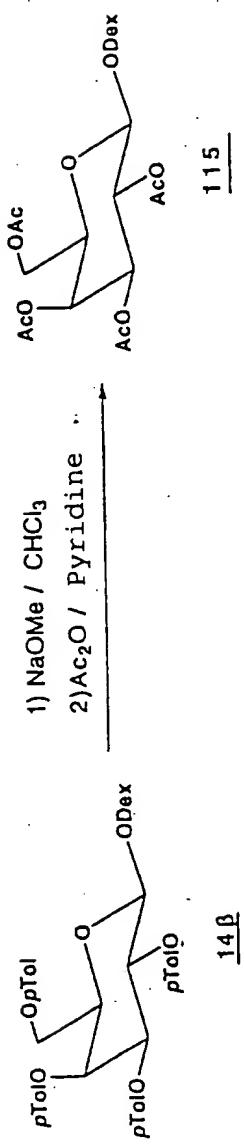


Fig. 2 6

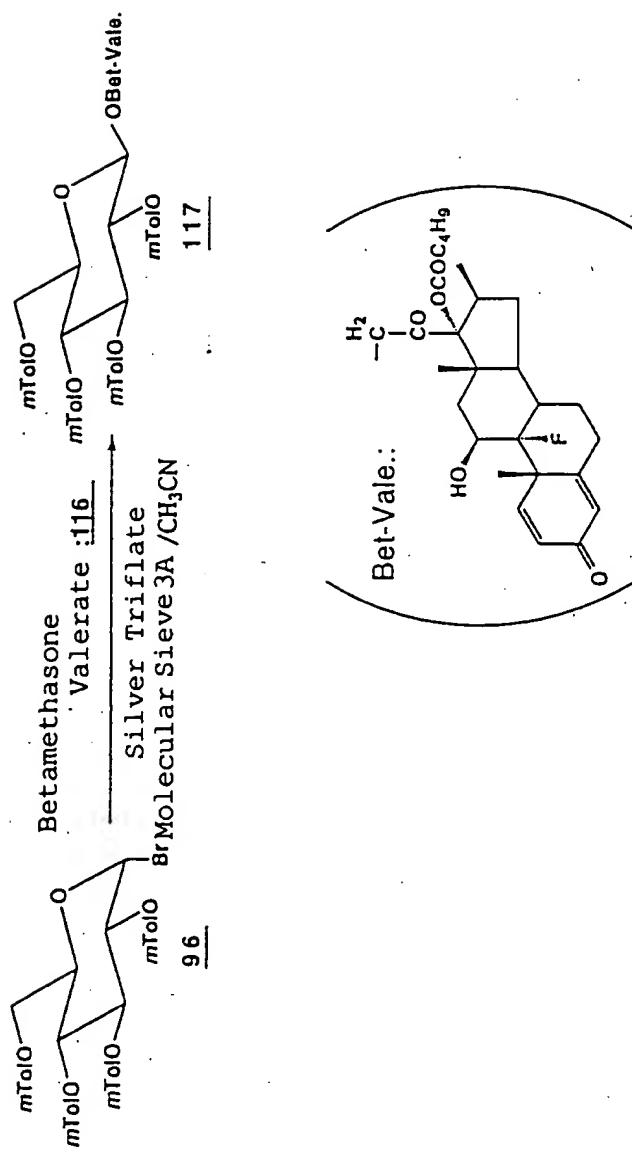


Fig. 27

